

Abstracts

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Plenary Lectures

PL1

"RANKL and RANK: Bone and beyond"

Josef Penninger

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RANKL was identified as an osteoclast differentiation factor as well as a T cell-derived stimulator of dendritic cells. The essential role of RANKL in osteoclastogenesis has been genetically proven in both mice and humans. In addition, RANKL was shown to play a critical role in various tissues including the thymus, gut, and mammary gland. The fully human monoclonal antibody against RANKL, denosumab, has been successfully utilized and approved for the treatment of bone metastasis and osteoporosis. We also studied the mechanism of bone destruction in rheumatoid arthritis and proposed that RANKL is a key therapeutic target for arthritis-associated bone destruction. Recently, denosumab has been indeed approved for rheumatoid arthritis in Japan. I will discuss the function of RANKL in multiple tissues and introduce recent findings providing an evolutionary perspective of RANKL/RANK signaling.

PL2

Abstract not available

PL3

Glucocorticoid rhythms, stress response and the brain from neonates to adults

Stafford Lightman

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Biological systems are invariably dynamic, with both stochastic interactions and deterministic processes across multiple timescales ensuring the maintenance of homeostatic regulation and allowing us to adapt to changes in both internal and external environments. It is no surprise therefore that the stress responsive hypothalamic-

pituitary-adrenal (HPA) axis shows multiple levels of regulation which come together to regulate oscillating levels of glucocorticoid secretion with both diurnal and ultradian rhythmicity.

I shall describe the mechanisms underlying the HPA pulsatility and how these interact with higher level circadian control by the hypothalamic suprachiasmatic nucleus. I will show how the adrenal adapts to pulsatile ACTH and how tissues respond to pulsatile changes in cortisol/corticosterone. The importance of this for optimal emotional and cognitive function in man will be described. Finally, I shall describe novel technology allowing repeated measures of glucocorticoid hormones in infants undergoing cardiac surgery without the need for blood sampling.

PL4

Abstract not available

PL5

Nutrition and the reproductive axis: Implications for the control of puberty

Manuel Tena-Sempere

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Puberty is under the precise control of sophisticated regulatory networks, which integrate a large number of endogenous and environmental signals, including metabolic and nutritional cues. Thus, puberty onset is tightly bound to the state of body energy reserves, and deregulation of energy/metabolic homeostasis is often associated with alterations in the timing of puberty. However, despite recent progress in the field, our knowledge of the specific signals and central molecular mechanisms whereby puberty onset is modulated by metabolic factors remains fragmentary and incomplete.

Compelling evidence, gathered over the last fifteen years, supports an essential role of hypothalamic neurons producing kisspeptins, encoded by *Kiss1*, in the neuroendocrine control of puberty. Kiss1 neurons are major components of the hypothalamic GnRH pulse generator, whose full activation is mandatory pubertal onset. Kiss1 neurons seemingly participate in transmitting the regulatory actions of metabolic cues on pubertal maturation. However, the modulatory influence of metabolic signals (e.g.,

leptin) on Kiss1 neurons might be predominantly indirect and likely involves also the interaction with other transmitters and neuronal populations.

We will review herein recent work of our group addressing the molecular mechanisms whereby Kiss1 neurons are modulated by metabolic signals, thereby contributing to the nutritional control of puberty. Specially, the roles of the energy/metabolic sensors, AMP-activated protein kinase (AMPK) and SIRT-1, in the metabolic control of Kiss1 neurons will be discussed. Our data demonstrate that AMPK and SIRT1 operate as central regulatory hubs within Kiss1 neurons to transduce the effects of both sub-nutrition and obesity on puberty onset, by repressing or activating Kiss1 expression. These findings are posed of translational interest, as perturbations of these molecular pathways may contribute to the alterations of pubertal timing linked to conditions of metabolic stress in humans, ranging from malnutrition or obesity, and might become druggable targets for better management of pubertal disorders.

PL6

Abstract not available

PL7

Pituitary Gigantism – An Update

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Pituitary gigantism is a rare disorder caused by excess of GH/IGF-1 due to GH-secreting lesions, that occurs before epiphyseal closure leading to increased linear growth. These cases have more aggressive features of pituitary disease than sporadic acromegaly, including a younger age at disease onset and larger tumor size, and they can be challenging to treat. Over the past two decades several molecular defects that cause GH-secreting pituitary adenomas have been identified, including multiple endocrine neoplasia syndromes type 1 and 4, Carney complex, McCune-Albright syndrome, familial isolated pituitary adenoma (FIPA) and AIP mutations, pituitary adenoma with paraganglioma/pheochromocytoma, and the recently identified X-linked acrogigantism syndrome (X-LAG). About half of pituitary gigantism cases have genetic predisposition, and AIP mutations represent the most frequent genetic cause of pituitary gigantism (29%). X-LAG is a novel pediatric syndrome due to chromosome Xq26.3 microdeletions involving GPR101. X-LAG can be caused by variable degrees of somatic mosaicism for GPR101 duplication in sporadic males. X-LAG accounts for 10% of pituitary gigantism cases and 80% of early-onset pediatric gigantism. Hypothalamic GHRH hypersecretion can accompany the pituitary abnormalities seen in X-LAG, and *in vitro* studies showed that GHRH receptor antagonist can significantly reduce GH release. Besides sporadic cases,

X-LAG represents a new genetic cause of non-AIP FIPA, transmission from affected mother to affected son was reported in 3 FIPA families. X-LAG is more frequent in females, and associated with early-onset pituitary disease (in most cases during the 1 year of life, and always before age of 5) and extremely accelerated linear growth. X-LAG is usually associated with markedly elevated GH and prolactin secretion by mixed pituitary adenomas/hyperplasia. Response to somatostatin analogs is poor and multimodal treatment is frequently required, including neurosurgery, GH receptor antagonist and radiotherapy, which however increase the risk of hypopituitarism.

PL8

Novel advances in artificial pancreas development

Boris Kovatchev

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In 2018, the National Library of Medicine (PubMed) included 132 publications in the artificial pancreas (AP) field, and in the first 6 months of 2019, new 80 papers were published. This continues a trend of over 100 scientific publications per year since 2015 and confirms the growing prominence of the AP for the treatment of diabetes. This presentation recounts briefly the technologies enabling the AP, including continuous glucose monitoring (CGM) and automated control algorithms, and then discusses the latest results from Protocol 3 of the International Diabetes Closed-Loop Trial (NCT 03563313), which tested the new Control IQ system from Tandem Diabetes Care.

Control-IQ uses a Dexcom G6 CGM that does not require fingerstick calibrations, and a control algorithm originally developed at the University of Virginia, which modulates basal rate, administers automated insulin corrections, and has a dedicated safety system to anticipate and prevent hypoglycemia. Protocol 3 is the largest AP study attempted to date, executed at 7 sites in the United States enrolling N=168 participants with type 1 diabetes randomized 2:1 to Control IQ vs. sensor-augmented pump therapy (SAP), each participating for 6 months. All 168 participants concluded the study and now continue to use the system in a protocol extension. First results were revealed at the 2019 Scientific Sessions of the American Diabetes Association, showing that Control IQ was significantly (all p-levels <0.001) superior to SAP according to all accepted CGM metrics of glycemic control, including time in range, frequency of hypoglycemia and hyperglycemia, average glucose, glycemic variability, as well as HbA1c.

We can therefore conclude that, a century after the discovery of insulin, viable AP technology is within reach and entering the mainstream clinical practice. The AP is here to stay, and is on its way to fulfil its promise as the digital-age optimal treatment for diabetes.

Symposia

Novel Advances in Diabetes and Obesity

S1.1

Off the Weight Curve – Dynamics of Childhood Obesity

Antje Körner

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The development of obesity begins early in life. From our large observational studies we know that the age between 3–6 years appears critical for development of obesity in children and once established, childhood obesity regularly persists into adulthood leading to premature morbidity and even mortality. In addition to the mere expansion of fat mass with developing childhood obesity, there are alterations in adipose tissue function such as adipocyte hypertrophy, inflammation and fibrosis in adipose tissue depots, and an imbalance in adipokine secretion. This adipose tissue dysfunction is related to, and likely to contribute to, the early manifestation of clinical obesity-related comorbidities already emerging in the children.

Epidemiological studies have identified parental overweight, social deprivation and perinatal factors followed by the classical life-style factors as major risk factors for childhood obesity. Nevertheless, the mechanisms remain incompletely understood and include interplay of genetic, epigenetic and environmental factors. We have studied the functional role for some of such factors at the level of the adipose tissue to better understand the mechanisms behind the mere risk associations for childhood obesity.

S1.2

The Gut Microbiome and Obesity

Frank Scott

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The obesity pandemic is likely multifactorial, comprised primarily of reduced caloric expenditure and increased caloric intake secondary to dietary changes, coupled with host genetic predisposition and other environmental exposures. The role of the host microbiome in metabolism, energy expenditure, and metabolic disorders, including obesity, has more recently come under scrutiny as well. For example, several perturbations in the host microbiome have been associated with obesity.

The multitude of bacteria that comprise the human gut microbiome can interact with host metabolism and promote obesity

through several pathways. Firstly, the gut microbiome can digest dietary components that otherwise would not provide significant caloric intake for the host, potentially increasing caloric absorption by up to 10 percent. One classic example of this is the digestion of dietary fibers by gut bacteria, with conversion to short-chain fatty acids. Secondly, the microbiome interacts closely with the host intestinal innate immune system, which may also modulate host metabolism. Such regulation and increase or decrease metabolic demands, while also modifying distances for nutrient diffusion dependent on the degree of inflammation present.

Several factors can also modify the host microbiome, indirectly affecting the host metabolism and promoting weight gain. This is classically described in the agricultural industry, where antibiotics have been exploited for decades to promote weight gain among various livestock. More recently, several murine and human epidemiologic studies have suggested a similar role for antibiotic exposure early in life and pediatric-onset obesity. Lastly, there are multiple active studies assessing how we might be able to modify a person's bacterial composition in order to advantageously affect their metabolic derangements.

S1.3

Rare genetic forms of obesity: clinical approaches and current treatments in 2019

Christine Poitou

INSERM, Nutriomics UMR_S U1166, University Pierre et Marie Curie, Institute of Cardiometabolism and Nutrition (ICAN) Assistance Publique-Hôpitaux de Paris, Nutrition Department, French Reference Centre for Prader-Willi Syndrome, Paris, France

Obesity—defined as excess fat mass which impacts on physical health—is a complex and multifactorial disease where numerous environmental factors (overeating and/or reduced physical activity) act in concert with genetic factors. Understanding molecular mechanisms of obesity has rapidly improved in recent years due to the development of faster, more specific genetic screening tools (1). Rare genetic obesities are distinguished from more-common polygenic obesities where multiple susceptibility genes with slight individual effects combine to modify weight. Cumulative genetic contributions can be amplified by ‘obesogenic’ lifestyles (overeating feeding, sedentary living, stress, etc).

Genetic obesities can present with different clinical symptoms depending on the genes involved; a) monogenic obesities with rare early-onset obesity combined with abnormal feeding behavior and endocrine disorders, and which are mainly due to autosomal recessive mutations in genes of—or associated with—the leptin/melanocortin pathway, which plays an essential role in the hypothalamic control of food intake; b) over 100 syndromic obesities corresponding to severe early-onset obesity with additional phenotypes (intellectual disability, dysmorphic features, and organ-specific developmental abnormalities), such as the most frequent Prader-Willi (PWS) and Bardet-Biedl (BBS) syndromes; and c) oligogenic obesity, such as melanocortin 4 receptor (*MC4R*)-linked obesity, characterized by a varying severity of obesity, partly dependent on environmental factors, and the absence of specific phenotype.

It is vitally important to diagnose genetic forms of obesity as specific management provided by specialized and multidisciplinary teams, is needed as soon as possible (from early childhood) (1). Early diagnosis and management of these rare obesity forms should enable improved prognosis into adulthood. Nevertheless, the transition between pediatric care and adult specialists remains a critical point in time, and is often associated with medical and social breakdowns (2). Current active research has identified several promising therapeutic molecules and target pathways for genetic obesities, which should change the prognosis for these rare severe forms of obesity (3-6).

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Novel Mechanisms and Therapies in Bone and Growth Plate: Investing in the Future Health of Children

S2.1

Abstract not available

S2.2

Anabolic Therapies for Osteoporosis in Childhood

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The medical treatment of osteoporosis in children at present mainly relies on anti-resorptive drugs, in particular bisphosphonates. However, not all forms of pediatric osteoporosis are characterized by increased bone resorption. In disorders with low bone turnover and decreased bone formation activity, such as osteoporosis due to neuromuscular disorders and glucocorticoid exposure, use of bone anabolic approaches appears to be a more logical option than anti-resorptive drugs, which further suppress bone turnover. Several bone anabolic approaches to treat osteoporosis are available and can be categorized as hormone therapy, mechanical stimulation, and biologic anabolic (antibody) therapy. Treatment with growth hormone, androgens and parathyroid hormone are some of the hormonal approaches. Among mechanical therapies, whole body vibration has been tested in several conditions. Antibody-based

therapies, such as inhibition of sclerostin and transforming growth factor beta, have not yet been tested in children but represent potentially the most specific approach to induce bone formation. Nevertheless, such treatments can be expected to have only a short-lived effect on bone. Long-acting osteoporosis therapy may therefore still be required.

S2.3

Glucocorticoid-Induced Osteoporosis in Children: Targeting the Spine in Osteoporosis Diagnosis, Monitoring and Treatment

Leanne M. Ward

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Despite significant advances in the medical management of childhood diseases, glucocorticoids (GCs) continue to be the mainstay of therapy for numerous serious conditions, including hematological malignancies, Duchenne muscular dystrophy (DMD) and inflammatory disorders. In order to understand the natural history of bone development in GC-treated children, a pan-Canadian longitudinal observational research study called “STOPP” (STeroid-induced Osteoporosis in the Pediatric Population) was launched in the last two decades. The STOPP study revealed a number of key biological principles about pediatric GC-induced osteoporosis (GIOP); among the most important was that vertebral fractures are the clinical signature of GIOP in children, an observation which unveiled the vulnerability of the pediatric trabecular-rich spine to the toxic effects of GCs.

By showing that vertebral fractures in GIOP are linked to biologically logical predictors including back pain, bone mineral density and an increased risk of future fractures, the STOPP Consortium validated that > 20% loss of vertebral height ratio defines a vertebral fracture in children, a decision that can be aided in equivocal cases by qualitative signs of vertebral fracture such as loss of endplate parallelism, endplate interruption and in older children, anterior cortical buckling. Reshaping of vertebral fractures (i.e. restoration of normal vertebral dimensions) is a key sign of recovery from GIOP, a phenomenon that occurs in the absence of osteoporosis therapy among children with significant residual growth potential, and transient GC exposure (such as younger children with leukemia). On the other hand, persistent bone health threats (such as in DMD), or GC exposure in older children with less growth potential, both mitigate the potential for vertebral body reshaping and can lead to permanent vertebral deformity if treatment is not initiated in a timely fashion. Current evidence suggests this is an important adverse outcome of pediatric GIOP, given observations that adults with vertebral fractures due to osteoporosis have reduced pulmonary function compared to those without.

Together, these findings underscore the importance of early identification and treatment of vertebral fractures in children at risk for permanent vertebral deformity, either due to older age or aggressivity of the GC exposure. Intravenous (IV) bisphosphonate therapy is a safe and effective first-line therapy for treatment of GC-induced vertebral fractures. However, IV bisphosphonates do not completely rescue the phenotype in the most aggressive forms of GIOP, an observation that opens the door to novel strategies.

Disclosures: Previously participated in a clinical trial with Merck. Currently a consultant to and participating in clinical trials with Novartis and Amgen, with funding to Dr. Ward's institution.

Novel Insights in Our Understanding of Disorders of Sex Development: From Genes to Clinical Outcomes

S3.1

Abstract not available

S3.2

Abstract not available

S3.3

Novel insights into sex determination: mutual antagonism of pro-testis and pro-ovary signalling pathways

Andy Greenfield

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There is no single conception of sex that covers the multitude of biological processes that are commonly encompassed by the term and its cognates. Gonadal sex determination is sometimes known as 'primary' sex determination due to its centrality in our understanding of 'maleness' and 'femaleness'. In mammals, this is characterised by the sexually dimorphic development of an initially bipotential gonadal primordium in the fetus into either a testis or an ovary. The development of a testis most commonly requires the expression of SRY from the Y chromosome in order to initiate a cascade of gene expression, much of which functions to oppose the influence of pro-ovary signals. If SRY expression is disrupted, varying degrees of XY gonadal sex reversal are observed, with attendant consequences for the phenotypic sex of the individual. Mutual antagonism between the pro-testis and pro-ovary pathways is found at the heart of the sex-determining mechanism. I will discuss recent advances in our understanding of the cellular and molecular basis of this so-called 'battle of the sexes' during gonad development, with an emphasis on signalling pathways required for testis determination in mice and humans.

ISPAD/Complications of Type 1 Diabetes

S4.1

Hypoglycemia in children with T1D: Past, Present, and Future

David Maahs

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Among the many complications of type 1 diabetes (T1D), hypoglycemia is an acute concern for children with T1D and their families. Moreover, fear of hypoglycemia is a common barrier to achieving glucose targets. Numerous advances in care have been made since the Diabetes Control and Complications Trial was published in 1993 in which lower HbA1c was associated with increasing risk of severe hypoglycemia. More recent data indicate that lower HbA1c (7% ISPAD target) can be achieved without increasing the risk of severe hypoglycemia. Epidemiologic and clinical trial data will be reviewed to provide a historic and contemporary assessment of hypoglycemia in children with T1D. We are in the transition from blood glucose meters to continuous glucose monitors (CGM) and these improved tools for patients, families and clinicians can reduce the risk of hypoglycemia. Advances in insulin action, increased use of insulin pumps, and the advent of automated insulin delivery and their relationship to hypoglycemia will be discussed. Novel formulations of glucagon are in development and their clinical availability will add to our ability to prevent and treat hypoglycemia. These numerous advances have resulted in a beneficial impact on hypoglycemia in children with T1D. However, further advances are needed to improve care and reduce the burden of hypoglycemia on children with T1D and their families. Moreover, these advances must be made available to all children with T1D worldwide.

S4.2

Novel advances in diabetic retinopathy screening and management

Kim Donaghue

Children's Hospital at Westmead, Sydney, Australia

Screening for diabetic retinopathy has been expanded from ophthalmology-based assessments. Retinal photography can be used in primary care by trained photographers, and then graded by trained staff using Telemedicine. Ultrawide retinal cameras can now capture over 80% of the retina from a single image. It may be more predictive of progression to proliferative retinopathy than the traditional views, but cost of equipment for benefit is unclear. There have been advances in Deep Learning for retinopathy grading which have been well studied from standard datasets and in study populations. Failure rate of retinal photography requires more face to face assessment. Optical coherence tomography

(OCT) is useful for measurement of retinal thickness and detection of macular oedema. There are also more portable devices for retinal screening for diabetic retinopathy.

At the same time we are learning more about risk factors and biomarkers, which may help define more appropriate screening intervals for retinopathy progression. There are promising results of albumin creatinine ratio as a biomarker of increased risk for retinopathy progression from the AddIT study. Another promising biomarker is retinovascular geometry with initial vasodilation of arterioles and venules over the standard central field. Vitreous biomarkers have been shown to be angiogenic (VEGF) and antioangiogenic.

Anti-VEGF therapy used frequently and administered intraocularly has been shown to be superior to Laser therapy with less side effects. Laser panretinal photocoagulation therapy reduces peripheral vision, colour vision, contrast sensitivity, and night vision.

Prevention remains the major focus of diabetes management with glycaemic control and longer duration the major determinants of disease and loss of vision. Blood pressure control may reduce risks of severe disease.

S4.3

Prediction of renal and cardiovascular complications

Loredana Marcovecchio

University of Cambridge, UK

Vascular complications continue to be a major concern for young people with type 1 diabetes (T1D), who have a decreased life expectancy, by 8-16 years, compared to the background population. Diabetic nephropathy and cardiovascular disease are main contributors to morbidity and mortality in people with T1D. Thus, early detection and prevention of complications are of paramount importance to improve their long-term prognosis.

Although HbA1c is a major risk factor, and the main focus of current screening and treatment strategies, suboptimal glycaemic control is a common problem among young people with T1D, and there is a clear need for improved markers to identify subjects at risk. Evidence is accumulating that early increases in urinary albumin excretion, still within the normal range, could identify adolescents with T1D who are at an increased risk of complications, independently of HbA1c. In young people with childhood-onset T1D, early increases in urinary albumin excretion can occur during the first years after diagnosis and they can predict future risk of vascular complications. Recent data from the cohort of adolescents recruited into the Adolescent type 1 Diabetes cardio-renal Intervention Trial (AddIT) support the value of albumin excretion as an early renal, retinal and cardiovascular marker. In the AddIT cohort of around 800 adolescents with T1D, an albumin excretion in the top tertile of the normal range was associated with renal outcomes, such as microalbuminuria and hyperfiltration, as well as with a worse cardiovascular profile and retinopathy progression during a 2-4 years follow-up period. These data support the concept that risk stratification using urinary albumin excretion during early adolescence may be critical for the early identification of patients at risk of vascular complications, and to guide the implementation of preventive and treatment strategies.

Impact of Genomics on Growth

S5.1

Novel insights into genetic disorders of growth

Jesús Argente

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Human growth is a very complex phenomenon that is influenced by genetic, hormonal, nutritional and environmental factors from fetal life throughout puberty. Although the GH-IGF axis clearly has a central role in this process, with specific actions on longitudinal growth, numerous other genes are also involved in determining stature. Indeed, genome-wide association studies have identified >600 variants associated with human height, but this still only explains a small fraction of phenotypic variation. Since short stature in childhood is a common reason for clinical referral, pediatric endocrinologists must be aware of the multifactorial and polygenic contributions to height. Multiple disorders characterized by growth failure of prenatal or postnatal onset due to single gene defects have been described. Their early diagnosis, facilitated by advances in genomic technologies, is of upmost importance for their clinical management and to provide genetic counseling. In this conference the current clinical and genetic information and new taxonomic classification regarding isolated GH deficiency, combined pituitary hormone deficiency, GH insensitivity and primary peripheral deficiencies including IGF1, IGFALS, IGF1R, IGF2 and PAPP-A2 will be reviewed. In addition, different syndromes with proportionate short stature as the main feature, including syndromes with short stature and microcephaly (Seckel syndrome spectrum disorders –SSSD-, microcephalic osteodysplastic primordial dwarfism –types I and II-, 3M syndrome, Meier-Gorlin syndrome) will be discussed. Special attention will be given to the recently described abnormalities in the genes *RNPC3* and *PAPP-A2*. Two important questions that should be discussed among pediatric endocrinologists and geneticists include: 1) Who should be tested for short stature and genetic alterations? and 2) What genetic techniques should be used for the best diagnosis? This conference will highlight these questions.

S5.2

SHOX: From Basic Research to Complex Models and Therapy

Gudrun Rappold

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SHOX deficiency is the most frequent genetic growth disorder associated with isolated and syndromic forms of short stature. Caused by mutations in the homeobox gene SHOX, its varied clinical manifestations include isolated short stature, Léri-Weill

dyschondrosteosis, and Langer mesomelic dysplasia. In addition, SHOX deficiency contributes to the skeletal features in Turner syndrome. Causative SHOX mutations have allowed downstream pathology to be linked to defined molecular lesions. Expression levels of SHOX are tightly regulated, and almost half of the pathogenic mutations have affected enhancers. Clinical severity of SHOX deficiency varies between genders and ranges from normal stature to profound mesomelic skeletal dysplasia. First genetic modifiers have been described. Treatment options for children with SHOX deficiency are available. Two decades of research support the concept of SHOX as a transcription factor that integrates diverse aspects of bone development, growth plate biology, and apoptosis. Due to its absence in mouse, the animal models of choice have become chicken and zebrafish. These models, therefore, together with micromass cultures and primary cell lines, have been used to address SHOX function. Pathway and network analyses have identified interactors, target genes, and regulators. Recent data will be summarized and insight given into the critical molecular and cellular functions of SHOX in the pathogenesis of short stature and limb development.

S5.3

The role of KCNQ1 in pituitary development

Taneli Raivio

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Childhood onset of growth hormone deficiency (GHD) is a clinically heterogeneous condition and defining its cause is important for diagnostics and treatment. The most common genes implicated in the genetic etiology of growth hormone deficiency (GHD) are *GH1* (MIM: 139250), encoding growth hormone (GH), and *GHRHR* (MIM: 139191), encoding the receptor for GHRH. GHD may also result from mutations in genes that encode transcription factors involved in pituitary development: *OTX2* (MIM: 600037), *SOX2* (MIM: 184429), *SOX3* (MIM: 313430), *LHX3* (MIM: 600577), *HESX1* (MIM: 601802), *PITX2* (MIM: 601542), *PROPI* (MIM: 601538), *POU1F1* (MIM: 173110), and *TCF7L1* (MIM: 604652) (1-3). Additionally, mutations in *RNCP3*, a gene which encodes the minor spliceosomal protein U11/U12-65K, are shown to underlie growth hormone deficiency (4). Some of the mutations in the genes above are associated with additional pituitary hormone deficiencies and developmental abnormalities, such as variants of septo-optic dysplasia (MIM: 182230), ocular defects, ectopic posterior pituitary, skeletal defects, and intellectual impairment. We have recently shown that two missense mutations, p.(Arg116Leu) and p.(Pro369Leu) in *KCNQ1*, a gene implicated in cardiac arrhythmias, underlie growth hormone deficiency and maternally inherited craniofacial phenotype with gingival fibromatosis (5). Subsequently, children with long QT syndrome due to loss-of-function mutations in *KCNQ1* were shown to grow normally (6), and *KCNQ1* mutations were not found in a cohort of 53 patients with GH-secreting pituitary adenomas (7). In conclusion, the role of ion channels in the regulation of human growth has

started to emerge. My laboratory currently focuses in elucidating the molecular mechanism by which the two *KCNQ1* mutations cause pituitary hormone deficiency.

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Endocrinology Meets Diversity: Transgender Youth

S6.1

Impact of cross-sex hormone treatment on structural brain networks

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Sex-steroid hormones such as testosterone and estradiol play a key role in sexual differentiation during gestation but exert also strong effects on the body and the brain during puberty or even in adulthood. In addition, influences on cognition and emotional processing are frequently reported. The investigations of transgender people undergoing cross-sex hormone therapy provide a unique model for studying those effects on gray and white matter brain structure *in vivo* by using the technique of structural magnetic resonance imaging (MRI) and diffusion-weighted imaging (DWI). The investigation of white matter brain structure using DWI in 29 female-to-male (FtM) and 15 male-to-female (MtF) before treatment and after one and 4 months of continuous hormonal administration led to alterations in several white matter tracts. In FtMs, decreases in mean diffusivity (MD) and increases in fractional anisotropy (FA) values were detected, while in MtFs the opposite results were found (Kranz *et al.*, 2017). As the hypothalamus is thought to be crucially involved in hormonal regulation, changes were assessed in this specific brain region, again after those two time points in comparison to baseline. The analysis in 25 FtM participants showed unilateral MD reductions after 1 month and bilateral decreases after 4 months of treatment (Kranz *et al.*, 2018). Those results suggest androgenization-related effects in FtM and feminization-related changes in MtF. The assessment of gray matter changes due to hormonal administration after 4 months revealed widespread decreases in subcortical areas, most pronounced in the hippocampus for 14 MtF subjects, who received estradiol and anti-androgens (Seiger *et al.*, 2016). In addition, decreases in 18 FtMs were found in Broca's and Wernicke's areas with higher levels of bioavailable testosterone after one month explicitly in those areas related to speech and language processing. Simultaneously, a strengthening of the fiber tract connecting those two brain regions was observed (Hahn *et al.*, 2016).

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S6.2

Psychiatric comorbidities in Transgender Youth

Annelou de Vries

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I review the mental health difficulties that transgender and gender diverse children and adolescents may present with, specifically emotional difficulties. Many studies reveal depression scores and parent and self-reported measures of emotional and behavioral problems that are comparable to mental health clinic referred populations. Children and adolescents who feel that they are acknowledged and supported in their gender diverse feelings, e.g. by receiving gender affirming medical treatment or social transitioning, seem more resilient. In contrary, transgender youth who experience rejection and social ostracism seem more vulnerable for developing depressive, anxiety and suicidality symptoms. A specific concern in transgender care is the overrepresentation of autism within transgender youth. The possible link between autism and gender diversity raises diagnostic, treatment and theoretical questions that will be discussed. Results of various studies of the Amsterdam Center of Knowledge on Gender Dysphoria will illustrate the presentation.

S6.3

Gynecological aspects and fertility issues in transgender adolescents

Mick Van Trotsenburg

UniBureau genderPRO, Vienna, Austria. Universitätsklinikum St.Pölten-Lilienfeld, Lilienfeld, Austria

This presentation briefly gives an overview of typical gynaecological issues and fertility options of transgender adolescents.

Typical gynaecological complaints and treatment options will be addressed: e.g. amenorrhea induction prior to cross-sex hormones, irregular bleeding, dysmenorrhea, vaginal discharge but also the limitations of gynaecological examination in female assigned adolescents.

National and international organizations, including the World Professional Association for Transgender Health, American Society for Reproductive Medicine, and Endocrine Society have put forth guidelines recommending that transgender individuals are counselled about fertility preservation options prior to initiating gender-affirming treatment. But what to tell adolescents desperately seeking gender-affirmative treatment and anxious for delay of the transitional trajectory? And parents who often prioritize fertility preservation to maintain an open future for their child?

In adult transwomen, semen cryopreservation is typically straightforward but not for adolescents. Is sperm quality harvested at adolescent age sufficient to say with good conscience that expensive cryopreservation for up to 10 or 20yrs is worth the effort? At age 13 boys experience on average the first ejaculation and at age 17 on average normal spermatozoal motility is reached. For transwomen at adolescent age and prior to treatment sperm cryopreservation possible age-related altered sperm quality needs to be addressed. For transgirls under pubertyblocking treatment prior to cross-sex hormones semen cryopreservation is no option as it takes months for the HPA-axis to develop and stimulate spermatogenesis. ICSI or testicular tissue preservation, use of spermatogonium stem cells and in vitro-maturation are experimental and may be future options.

For adolescent transmen fertility preservation appears even more difficult. Oocyte cryopreservation include controlled ovarian hyperstimulation, and transvaginal ultrasound-guided ovarian puncture to harvest eggs. For transmen this procedure may cause great distress by interrupting androgen therapy and undergoing ovarian hyperstimulation. Moreover women with elevated androgens are at higher risk for OHSS. Alternatively ovarian tissue preservation may be performed at the same time as gender affirming surgery. Consecutively in-vitro maturation, IVF and embryotransfer either homo- or heterologously is warranted. For transmen at adolescent age it is likely that ovaries are not fully developed, and hyperstimulation and oocyte retrieval may not be fully successful.

Overall, it seems mandatory to discuss reproductive options and limitations, also at younger age being very clear about the limited knowledge and experience available possibly impeding with the principles of proper informed consent.

Adrenal Insufficiency: New Mechanisms, New Therapies

S7.1

Novel interventions to treat adrenal insufficiency

Leonardo Guasti

Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK

The generation of functional, long-lived adrenocortical cells through reprogramming from pluripotent stem cells or via lineage conversion strategies, could offer an alternative treatment modality for adrenal insufficiency (AI) due to a variety of causes, such

as mutation in steroidogenic enzymes as seen in congenital adrenal hyperplasia (CAH). The recent generation of human induced steroidogenic cells (hiSCs) from fibroblasts, blood- and urine-derived cells established from healthy donors and patients affected by CAH has provided a new paradigm for disease modelling and potentially cell therapy. For the latter, further research is needed using appropriate AI models. We will be discussing the design of reprogramming protocols compatible with clinical applications, the effort in establishing patient-derived adrenocortical organoids (which adrenocortical stem cell antigen can be used to generate organoids from a single cell?) and the application of gene editing technologies on adrenocortical cells *in vivo* or *ex vivo*.

57.2

Novel insights into the pathophysiology of adrenal insufficiency syndromes

John Achermann

UCL GOS Institute of Child Health, London, UK

Primary adrenal insufficiency (PAI) is an important diagnosis to make as it is potentially life-threatening and requires urgent treatment. Although most paediatric endocrinologists have experience of more common conditions such as congenital adrenal hyperplasia (CAH) and autoimmune adrenal insufficiency, more than 30 other genetics causes of PAI exist, as well as physical causes such as haemorrhage. Reaching a specific diagnosis for some of these rarer conditions can have important management implications, such as the need to assess potential associated features (or syndromes), modifying treatment approaches, counselling families about recurrence risk and identifying presymptomatic family members. New high-throughput sequencing approaches are increasing our knowledge in this area and are helping in the discovery of new genetic causes of PAI. Here, I will review several recent insights into the genetics of adrenal insufficiency and related molecular mechanisms, including: 1) the role of the nuclear receptors DAX-1 (NR0B1) and steroidogenic factor-1 (SF-1, NR5A1) in human adrenal and reproductive function; 2) non-classic forms of STAR and CYP11A1 insufficiency that present with delayed-onset PAI and are surprisingly common; 3) defects in SGPL1 causing a new sphingolipidosis that affects multiple systems; and 4) growth restriction syndromes affecting adrenal development such as gain-of-function of the growth repressors CDKN1C (IMAGE syndrome) and SAMD9 (MIRAGE syndrome), or loss of POLE1. The relative prevalence of some of these genetic causes of PAI in large cohort studies will also be discussed.

57.3

Widening the horizon - Clinical relevance of steroid hormone pathways

Stefan A. Wudy

University of Giessen, Germany

While it had been widely believed at the end of last century that most problems in steroid metabolism had already been solved, and not much more significant discoveries were to be expected anymore, recent exciting observations and rediscoveries have initiated a renaissance in steroid metabolism research. These revolutionary findings have often been initially made in animals and have also significantly been driven by new steroid analytical techniques based on mass spectrometry. Thus, the classical (canonical) concepts of human steroid metabolism have become shattered and new insights into physiology and pathology of steroid related disorders have been provided, which will open up new avenues in diagnosis and therapy of these entities. For instance, observations in the Tammar wallaby led to the discovery of a novel androgenic synthetic route leading to dihydrotestosterone. This so called “back door or alternative pathway” bypasses the classical routes via DHEA, 4-androstenedione and testosterone. Furthermore, a new class of steroids, 11-oxygenated androgens, such as 11-keto-testosterone, has for long been known in teleost (bony) fish presenting important androgens. But it has only been until recently, that we have begun to understand their new and important role in the human being, particularly in hyperandrogenic conditions such as premature adrenarche, CAH or PCOS. New insights have also been achieved regarding complex, conjugated steroids, particularly the group of steroid sulfates. The identification of the cell membrane bound Sodium-dependent Organic Anion Transporter SOAT, an uptake carrier specifically transporting sulfated steroids, permitted recognition of an intracrine regulatory mechanism via the sulfatase pathway. This mechanism is restricted to cells that express an uptake carrier and STS together with steroid receptors and has been studied in human breast cancer and reproductive processes. A further, exciting novel finding is first *in-vivo* evidence for the adrenal gland as a drug metabolizer. While it has been hitherto believed that drug metabolism in mammals is limited to the liver and its cytochromes P450, it could now be shown that there is no strict subdivision between P450s involved in exogenous and endogenous metabolism. This talk will summarize the most relevant recent discoveries in the field of steroid metabolism and will illustrate their clinical significance and potential by work from others and our own group.

Autoimmunity: From Diagnosis to Treatment

S8.1

New autoantibodies in endocrine autoimmunity development: Lessons from APECED

Pärt Peterson

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Patients with autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), develop autoantibodies to multiple self-proteins. The patients have high titer autoantibodies to multiple cytokines, most prominently to type 1 interferons and cytokines associated with Th17 cell functions. In addition to these signature autoantibodies, APECED patients develop autoantibodies to many other self-proteins characteristic to autoimmune diseases and display broad autoantibody repertoires with high inter-individual variations. These autoantibodies have gone through somatic hypermutation during their affinity maturation, and the autoantibody targets are enriched for evolutionarily conserved phosphoproteins, including tumor-specific autoantigens. Interestingly, the target autoantigens are not limited to proteins expressed in thymic medullary epithelial cells, and in contrast, many are expressed in lymphoid type of cells. Our findings support the hypothesis that specific protein properties contribute to the etiology of B cell autoimmunity.

S8.2

Monogenic forms of autoimmune diabetes: challenges and opportunities

Sarah Flanagan

University of Exeter Medical School, Exeter, UK

Monogenic autoimmune diabetes results from a single highly penetrant mutation that causes autoimmunity leading to destruction of the beta-cells. Identifying monogenic autoimmune diabetes can be a challenge; early-onset type 1 diabetes (T1D) can cluster with additional autoimmune diseases due to shared polygenic risk, particularly from the HLA DR3 and DR4 alleles, and islet and other organ specific autoantibodies are present in patients with both monogenic and polygenic aetiologies. Gene discovery approaches based on phenotype and family structure have had some success in monogenic autoimmune diabetes, with 11 genes described to date. Integration of genetic risk scores shows promise to improve the yield of gene discovery by removing more common clustering of T1D and additional autoimmunity.

Identifying novel causes of monogenic autoimmune diabetes provides insights into pathways of autoimmunity which can improve understanding of more common polygenic autoimmune disease. For patients, a diagnosis of monogenic autoimmune

diabetes is important as it can have treatment implications, with specific therapies for some subtypes (e.g. Abatacept in *LRBA* deficiency) and optimal immunosuppression in others (e.g. Sirolimus in IPEX syndrome). Furthermore, a genetic diagnosis is desirable before undertaking stem cell transplantation which can be curative but carries high risk. Families can also benefit from knowledge of recurrence risk and the availability of prenatal testing.

In 2014 we identified gain of function *STAT3* mutations as a cause of autoimmune diabetes with onset in the neonatal period. In 2017 we reported that recessively inherited *LRBA* mutations can cause autoimmune neonatal diabetes and more recently demonstrated that trisomy 21 can cause diabetes before 6 months that is autoimmune but not HLA associated. This suggests that there is a unique subset of diabetes caused by trisomy 21 amongst the more common co-incidence of T1D and Down syndrome.

S8.3

HSCT for genetically determined autoimmunity: hopes and pitfalls

Mary Slatter

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Haematopoietic stem cell transplantation (HSCT) is an established curative treatment for many primary immunodeficiencies (PIDs). Advances in donor selection, graft manipulation, conditioning and treatment of complications, mean that survival for many conditions is now around 90%. We now recognise an increasing overlap between disorders causing immune deficiency and immune dysregulation including autoimmunity. The most well known is IPEX (Immunodysregulation, polyendocrinopathy, enteropathy X linked) syndrome in which mutations in *FOXP3* lead to the absence of regulatory T cells resulting in unchecked effector T cell activation and organ specific autoimmunity such as diabetes, enteropathy, eczema and hypothyroidism. Outcome from transplant has been shown to be superior to conservative treatment with immunosuppression.

Next generation sequencing is leading to the identification of emerging disorders such as Cytotoxic T lymphocyte antigen 4 (CTLA-4) deficiency, phosphatidylinositol 3-kinase δ (PI3K-δ) syndrome and the Signal transducer and activator of transcription 1 or 3 gain of function disorders. These may present with endocrinopathies, enteropathy, inflammatory arthropathy and skin features as well as infections, lymphoproliferation and cytopenias. The challenge is to identify which patients may benefit from transplant and when to perform transplant in order to promote good long-term outcomes and quality of life.

Heterogeneity of Paediatric Diabetes

S9.1

Diversity in monogenic diabetes management and prognosis

Pål Rasmus Njølstad

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Monogenic forms of diabetes have specific treatments that differ from the standard care provided for type 1 and type 2 diabetes, making the appropriate diagnosis essential. Misclassification of all diabetes types may occur and healthcare providers should be aware of this possibility. A systematic approach to subjects who are newly diagnosed with diabetes can assist classification of common forms of diabetes and identify those in whom molecular investigation would be advantageous. There are clinical challenges to this end, including improving case-finding strategies, and understanding the interpretation of genetic variants as pathogenic, with clinically meaningful impacts. The main application of precision medicine is in the use of sulfonylurea agents in neonatal diabetes caused by mutations in K-ATP channel components and MODY due to mutations in HNF1A and HNF4A. These precision-based treatments not only achieve good glycemic control, but there is evidence demonstrating that they are superior to conventional approaches.

S9.2

Diagnostic and therapeutic implications of double diabetes

Tatsuhiko Urakami

Nihon University School of Medicine, Tokyo, Japan

Double diabetes (DD) is a term coined to describe individuals with evidence of islet-cell autoimmunity (type 1 diabetes: T1D) and showing obesity and insulin resistance (type 2 diabetes: T2D). The rising obesity trend that favors insulin resistance seems to have a role, in association with other environmental factors, for the development of islet-cell autoimmunity through different mechanisms. It has become apparent that more youth with T1D are overweight or even obese before hyperglycemia develops. Therefore, diagnosis of T1D is not always easy to place because the phenotypic manifestations typically coincide with T2D. In addition, obesity may contribute to the escalation of beta-cell destruction, as suggested by the accelerated hypothesis in individuals generally suspected as T1DM. Insulin resistance not only accelerates the apoptosis of beta cells but also renders them more immunogenic. Genetic factors associated with obesity also accelerate beta-cell function failure. In many cases, common pathogenic processes in T1D and T2D may be evident. SEARCH reported that youth diagnosed with T1D, who had autoantibodies to beta cells, exhibited a higher prevalence of overweight, but not obesity, than nondiabetic youths (1).

Gluffrida et al. (2) reported that one-third of patients with T1D had overweight/obese during follow-up, and we also found 27% of those had BMI more than 25 during follow-up. Increasing tendency of childhood overweight/obese worldwide may contribute to increase the number of DD.

Therapeutic approach for DD should include lifestyle modifications, including diet and physical activities. High-dose insulin due to insulin resistance may aggravate overweight/obese. Some oral hypoglycemic drugs, such as metformin and SGLT2 inhibitors, can be used in combination with insulin therapy. We experienced effectiveness of these drugs, which improved glycemic control with reductions of body weight and insulin doses in some cases.

References

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S9.3

Obesity Distorting Childhood Diabetes: Is it Type 2, Type 1, or MODY? A Pathophysiological Perspective

Silva Arslanian

UMPC-Children's Hospital, Pittsburgh, USA

There are modifiable and unmodifiable risk factors for youth type 2 diabetes (T2DM). Unmodifiable risk factors include genetics/epigenetics, minority race/ethnicity, and puberty. The major modifiable risk factors for youth T2DM are obesity and lifestyle habits of excess nutritional intake and decreased energy expenditure. Thus, in making a clinical diagnosis of T2DM, the major diagnostic criterion, at least in North America and Europe, is overweight/obesity. However, with the increasing rates of obesity in children with autoimmune type 1 diabetes (T1DM) and individuals with MODY, the clinical distinction between youth with T2DM and obese youth with autoimmune T1DM or MODY is difficult and imperfect. The distinction between youth with T2DM and T1DM is further blurred because, not infrequently, youth with T2DM present with diabetic ketoacidosis. Several hypotheses and terminologies have been proposed, such as hybrid diabetes, double diabetes, diabetes type 1.5, and latent autoimmune diabetes of youth, to refer to this subset of young patients with a clinical phenotype consistent with T2DM and evidence of autoimmunity consistent with T1DM. While laboratory assessment for islet autoimmunity could be of value to distinguish the different types of childhood diabetes, currently available commercial assays are not always sufficiently sensitive to detect low antibody titers, yielding negative results when in fact the patient may have autoimmune diabetes.

This lecture will present a pathophysiological perspective to unravel the differences in insulin sensitivity and b-cell function characteristic of each type of diabetes despite obesity changing the face of childhood diabetes. Moreover, novel data with respect to longitudinal changes in the pathophysiological alterations of glucose homeostasis distinctive for each may further clarify this heterogeneous picture.

Brain Development and Sex: Is it Chromosomes or Hormones?

S10.1

Multifaceted Origins of Sex Differences in the Brain

Erin Reinl, Margaret McCarthy

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Sex is one of the strongest biological factors influencing neural development, and yet our understanding of the molecular underpinnings of sexual differentiation is only just beginning. Just like the bipotential gonads, which only differentiate upon expression of SRY in XY males, the brain is also bipotential and differentiates due to a combination of genetic, epigenetic, environmental, and hormonal exposures. A period of testosterone production by the testes, which occurs as early as the second trimester in humans and during the late embryonic and early postnatal period in rodents, defines a critical period of sexual differentiation that drives the organization of enduring differences in circuitry and neuroanatomy between male and female brains. In the absence of gonadal hormones during this period, the brain develops in a female-typical fashion but is sensitive to masculinization by treatment with exogenous hormones. The cellular and molecular mechanisms induced by testosterone (converted to estradiol in the brain) are multifaceted and include neurogenesis, cellular differentiation, axon guidance, synaptic pruning, apoptosis, and phagocytosis. These pathways are both guided by and impact neurons and astrocytes. However, we have also found surprising roles for the immune system, including the innate immune cells of the brain, microglia, and even peripheral immune cells, like mast cells, which play critical roles in establishing sex differences. Although hormones dominate as purveyors of brain sexual differentiation, there is emerging evidence that genetic contribution by the sex chromosomes, even beyond SRY expression, contribute as well, and our understanding of these mechanisms are only in their infancy. As interest in sex differences and inclusion of both sexes in preclinical research continues to grow, it is likely that the list of multifaceted and sometimes surprising mechanisms of sex differences will grow as well.

S10.2

Abstract not available

S10.3

How hormones impact on emotion and cognition — new insights from Magnetic resonance imaging

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Magnetic resonance imaging (MRI) of the brain in disorders of sexual development (DSD) is still relatively scarce despite the opportunities it offers for understanding the influence of sex hormones on emotion and cognition. In this talk I will give an update on current structural and functional MRI research in different DSDs such as Klinefelter syndrome, Turner syndrome, Congenital Adrenal Hyperplasia, or Familial Male Precocious Puberty. Finally, parallels will be drawn to current data sharing efforts in the MRI community and how such efforts may stimulate research and confidence in findings when sample sizes are small as in the DSD community.

Recent Advances in Our Understanding of Hypogonadotropic Hypogonadism

S11.1

Novel insights into developmental pleiotropy from genetic studies in Kallmann Syndrome

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Defects in the specification, migration and/or function of Gonadotropin-releasing hormone (GnRH) neurons gonadotropin-releasing hormone result in Kallmann Syndrome (KS), a rare genetic disorder characterized by hypogonadotropic hypogonadism and anosmia (lack of sense of smell). To identify new molecular causes of KS, we performed a systematic genetic interrogation via whole exome sequencing of KS families. Autosomal dominant loss-of-function mutations in TCF12, a transcription factor previously known to cause syndromic craniosynostosis was identified as a novel cause for KS. We observed no distinction in localization of the mutations observed in patients with KS to those previously reported with craniosynostosis. Additionally, 3/10 families display both KS and craniosynostosis indicating that TCF12 allelism per se is insufficient to explain the phenotypic variability. TCF12 now joins an emerging group of genes (FGFR1, SMCHD1, CHD7, SOX10) that result in both KS and distinct craniofacial abnormalities, suggesting a shared role of these proteins during GnRH development and craniofacial development.

S11.2

Novel insights into the regulation of reproduction using 3D-imaging in transparent fetuses and postnatal animals

Paolo Giacobini

Inserm U1172, Lille, France. University of Lille, Lille, France

GnRH-secreting neurons are unusual neuroendocrine cells, as they originate in the nasal placode outside the central nervous system during embryonic development, and migrate to the hypothalamus along the vomeronasal and terminal nerves. Postnatally these cells become integral members of the hypothalamic-pituitary-gonadal axis and they regulate puberty onset and reproduction through the release of GnRH into the pituitary portal blood vessels for delivery to the anterior pituitary.

Disruption of GnRH neuronal migration and/or defective GnRH synthesis and secretion leads to congenital hypogonadotropic hypogonadisms, a rare endocrine disorder characterized by absent or incomplete puberty resulting in infertility.

Herein, we detailed for the first time the 3-dimensional spatio-temporal distribution and organization of GnRH neurons in rodents from embryonic development to adulthood and studied in detail the interactions of GnRH neurons with multiple cell populations participating to the control of reproductive functions in mammals.

S11.3

Abstract not available

Special Symposia

SS1.1

E-Learning in Paediatric Endocrinology and Diabetes in Resource Limited Countries (RLC)

Boot AM, Bacopoulou F, Kalaitzoglou E, van Wijngaard CCM, Ng SM, De Beaufort C, Zacharin M, Chanoine JP, Majaliwa ES, Drop SLS, on behalf of the ESPE e-learning committee

University Medical Center Groningen, Groningen, Netherlands

The structure and design of the ESPE web portal (www.espelearning.org) is based on facilitating Problem-Based Learning (PBL). It consists of carefully designed problems that challenge medical students, residents, postdoc's to use problem solving techniques, self-directed learning strategies and specialty knowledge.

The ESPE e-learning web portal is an interactive learning environment for up to date topics in pediatric endocrinology and

diabetes consisting of chapters and problem solving cases. The General Content has been reviewed by international experts and offers thirteen categories consisting of fifty-seven chapters and fifty-five problem solving cases.

Within the ESPE-elearning web portal a separate module has been developed specifically for health care workers at three levels of health care (primary, secondary, tertiary) in Resource Limited Countries (RLC). This RLC module currently consists of sixteen chapters and twenty-five cases covering all major subjects of pediatric endocrinology including a large chapter on diabetes. The content has been reviewed by global experts representing the International Consortium Pediatric Endocrinology (ICPE) including ISPAD and GPED. Thanks to the collaboration of junior/senior native speaking colleagues the module is globally and freely accessible in 5 languages: English, French, Spanish, Swahili and Chinese.

The web portal can be used for self-study: refreshing/gaining more in-depth knowledge of pediatric endocrinology and for teaching: classroom case discussion (via projector), or in preparation for a course (blended learning). The website supports formative assessment by providing immediate feedback at questions, which raises motivation, gives more insight in progress of acquisition of knowledge and competencies and improves cooperation between students and teachers.

In conclusion, the ESPE e-learning is a free and globally accessible portal that provides up to date and relevant educational information on pediatric endocrinology and diabetes topics. It offers interactive learning strategies for self-directed learning or teaching; the RLC module in particular provides three stratified levels of care.

SS1.2

E-learning ESPE interactive case

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A 13 months old infant, presented with failure to thrive, untreated congenital hypothyroidism and pseudo-hypertrophy of limb muscles (i.e. Kocher-Debre-Semelaigne syndrome). The child had delayed motor and mental development. Thyroxin replacement therapy, as well as nutritional support, was initiated.

Two to three weeks after treatment introduction, the motor and cognitive developments were accelerated with striking improvement as if global growth was stopped and switched-on once levothyroxine was given.

This infant is one of the youngest patients reported to have this presentation.

Meet the Expert

MTE1

Holistic approach to the individual with DSD

Martine Cools

Ghent University Hospital, Ghent, Belgium. Ghent University, Ghent, Belgium

Management of DSD is a sensitive area within the field of paediatric endocrinology. On the one hand, major progress has been made in amongst others understanding the molecular genetic background and the germ cell cancer risk of certain DSD conditions. On the other hand, practices that were common in the past, such as early genital surgery have become strongly criticised and controversial nowadays, leaving clinicians as well as patients and their families with a lot of questions regarding optimal management. To address these, a lot of effort, including the voices from patient representatives, has been put in developing tools and guidelines to standardise diagnostic procedures and clinical care across centers and geographical areas. The aim of such international collaboration is to further raise quality of care and to allow for studying long-term outcomes of the new management paradigms through international registration and data collection. Central in this endeavour is the holistic approach to the individual with a DSD and the development of specialized multidisciplinary teams in which all members have their unique and indispensable roles. Patients and parents have a key role in these teams; therefore enhancing understanding of the condition and its consequences and respectful communication between all team members is considered the cornerstone of care.

In this session, we will illustrate this approach with some concrete examples derived from clinical practice. Learning objectives include to obtain an overview of the recent practice changes and their rationale, to become familiar with the diagnostic and management tools and guidelines that have recently become available for the clinician with an interest in DSD and to share experiences with alternative approaches for the management of atypical genitalia.

MTE 2

The interpretation of abnormal thyroid function in tests in children and adolescents

Carla Moran

Beacon Hospital, Dublin, Ireland. Institute of Metabolic Science, University of Cambridge, Cambridge, UK

Patients with discordant thyroid function tests (TFTs) are common clinical conundrums for the practising paediatric and adult endocrinologist. In order to avoid unnecessary investigation and treatment, a structured approach to the work up is required.

During this session I will use a case based approach to review common causes of discordant TFTs, such as confounding physiological and pathophysiological factors, analytical errors, binding protein abnormalities and genetic causes. I will also provide a practical algorithm to the initial investigation and further work up of such patients.

MTE 3

New international guidelines on Turner Syndrome

Claus H. Gravholt

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Turner syndrome (TS) affects 25-50 per 100,000 females and can involve multiple organs through all stages of life, necessitating a multidisciplinary approach to care. Numerous important advances have been noted during recent years. These advances cover all specialty fields involved in the care of girls and women with TS. This new international guideline is based on an international effort with emphasis on 1) diagnostic and genetic issues, 2) growth and development during childhood and adolescence, 3) congenital and acquired cardiovascular disease, 4) transition and adult care, and 5) other comorbidities and neurocognitive issues. Here, I will present the most important new advances in the care of Turner syndrome. Treatment with growth hormone (GH) during childhood and adolescence allows a considerable gain in adult height. SHOX deficiency explains some of the phenotypic characteristics in TS, principally short stature. Puberty has to be induced in most cases, and female sex hormone replacement therapy should continue during adult years.

The proper dose of hormone replacement therapy (HRT) with female sex steroids has not been established, and, likewise, benefits and/or drawbacks from HRT have not been thoroughly evaluated. In most countries it seems that the transition period from paediatric to adult care is especially vulnerable and the proper framework for transition has not been established. Likewise, no framework is in place for continuous follow-up during adult years in many countries.

During the transition period many young females opt out of longitudinal follow-up, probably because they feel well and cannot clearly see the need for continued medical surveillance, which has to be thoroughly and well explained to patients. However, osteoporosis, diabetes, both type 1 and 2, hypothyroidism, obesity and a host of other endocrinological diseases and conditions are seen more frequently in Turner syndrome in the long term. Prevention, intervention and proper treatment is only just being recognized. Hypertension is frequent and can be a forerunner of cardiovascular disease.

Morbidity and mortality is quite elevated and many conditions need to be vigorously and routinely checked for and diagnosed as early as possible in order to prevent long-term health consequences. Congenital and acquired heart related morbidity remain the leading cause of death in TS and much of this morbidity can be prevented.

MTE 4**Klinefelter syndrome - when should testosterone be started?**

Julia Rohayem

University Hospital Münster, Münster, Germany

Males with Klinefelter syndrome (KS) have impaired gonadal function due to sex chromosome aneuploidy (47,XXY), ultimately resulting in testicular atrophy and hypergonadotropic azoospermia, thus infertility. At what time serum testosterone (T) concentrations decline in affected individuals, thereby indicating lifelong replacement, is not predictable. An early testosterone treatment provides potential benefits with respect to body composition, neuro-muscular function and final height. However, exogenous sex steroids have suppressive effects on the patient's central hypothalamo-pituitary-gonadal (HPG) axis, thereby opposing a possible wish for future paternity.

KS males may have some euploid spermatogonial stem cells in their testicles. With onset of puberty, these cells enter meiosis, resulting in focal spermatogenesis. The elongated spermatozoa may be harvested (either from semen or via microsurgical sperm extraction procedures (mTESE)) and cryopreserved for future use in assisted reproduction, specifically intracytoplasmic sperm injection (ICSI).

We investigated HPG axis hormones in 281 KS males aged 10–25 years and 233 age-matched controls and analyzed semen in late pubertal subjects. In addition, the success of surgical sperm retrieval was determined in 50 late pubertal und 85 adult azoospermic KS patients.

Serum T concentrations of ≥ 10 nmol/L were achieved spontaneously in 62% of adolescent KS males and in 85% of controls ($T_{KFS}: 12.2 \pm 5.4$ vs. $T_C: 16.6 \pm 7.2$ nmol/L). LH_{KFS} concentrations were above the reference range, i.e. > 10 U/L in 84% of young KS males ($LH_{KFS}: 18.6 \pm 12.2$ vs. LHC: 3.5 ± 1.6 U/L). In 9/130 (7%) KS adolescents, few spermatozoa were found in semen, in contrast to normal adult sperm concentrations in 73% (46/63) of controls. The chances for successful surgical sperm retrieval decreased with age, with adolescents aged 15–25 having the highest chances (54%), if LH was ≤ 17.5 U/L and T ≥ 7.5 nmol/L.

There is a window of opportunity for harvesting and cryopreserving sperm in males with KS during late spontaneous puberty and young adulthood, potentially enabling future paternity. Testosterone replacement should rather not be started before exploration of the KS individual's reproductive potential.

MTE 5**Managing endocrinopathies in McCune-Albright Syndrome**

Daniele Tessaris

Pediatric Endocrinology, University of Torino, Regina Margherita Children Hospital, Torino, Italy

McCune Albright Syndrome (MAS, OMIM # 174800) is a rare congenital sporadic disorder with an estimated prevalence ranging from 1 in 1,00,000 to 1 in 100,000. MAS is caused by a post-

zygotic somatic activating mutation of the GNAS1 gene resulting in an increased GSα protein signaling leading to hyperfunction of glycoprotein hormone receptors, autonomous cell proliferation, and hormonal hypersecretion. The mosaic constitutive activation of this signal transducer is clinically evident with a scattered hyperfunction of endocrine tissues with a wide phenotypic spectrum. MAS classical phenotype includes the clinical triad of bone fibrous dysplasia (BFD), café-au-lait skin spots due to skin dysplasia, and peripheral precocious puberty (PPP). However other endocrinopathies as hyperthyroidism, hypercortisolism, hyperpituitarism, kidney phosphate wasting, can be present.

Precocious puberty (PPP): treatment prevents bone age advancement and compromise of adult height. For girls, the aromatase inhibitor letrozole is used; for boys, treatment options include aromatase inhibitor and androgens receptors blockers Thyroid disease:methimazole effectively manages hyperthyroidism; however, because hyperthyroidism is persistent, thyroidectomy is possible. Growth hormone excess: medical therapy is the preferred first-line treatment; options include (alone or in combination) octreotide and the growth hormone receptor antagonist pegvisomant. Hypercortisolism: treatment varies by the presentation of neonatal Cushing syndrome.

Surveillance of endocrinopathies is mandatory. Infants: clinical signs of hypercortisolism. All children: growth acceleration and other clinical signs of precocious puberty and/or growth hormone excess. Children: Age <5 years: thyroid function abnormalities. With thyroid abnormalities on ultrasound examination but normal thyroid function: periodic monitoring of thyroid function. Males: testicular lesions (physical examination and testicular ultrasound). Females: breast cancer (earlier than is recommended for the general population). Check routinely phosphorus levels related to age to correct phosphate wasting that can worsen bone quality and pain.

MTE 6**Insulin Dosing for Real Meals**

Matthew Campbell

University of Leeds, Leeds, UK

People with type 1 diabetes are provided guidance and structured education on adjusting their mealtime bolus insulin dose based on the carbohydrate content of the meal. However, recent research in patients using continuous subcutaneous insulin infusion (CSII) and Multiple Daily Injections (MDI) has highlighted the role of dietary fat in increasing prandial insulin requirements, particularly late into the postprandial period. The average daily amount of fat consumed as part of a westernised diet typically exceeds ~80g, with some habitual meals often consuming up to 50g of fat. Following intestinal absorption, fats ingested in the meal appear in the blood predominantly as triglycerides (TG; termed postprandial lipaemia), reaching a peak 3–4 hours' post-consumption before gradually decreasing. Prolonged and exaggerated postprandial lipaemia significantly increases CVD risk. TGs are transported in lipoproteins (chylomicrons and VLDL, and their respective remnants), which upon entry to the circulation undergo dynamic remodelling which is largely atherogenic. Thus, people with type 1 diabetes following westernised diets and using only

the carbohydrate counting method for mealtime insulin dosing are likely exposed to a repeated pattern of prolonged and exaggerated postprandial glycaemia, lipaemia, and cardiovascular risk. In this session, we will discuss novel strategies regarding insulin dosing for real meals.

MTE 7

Management of Graves' disease

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Managing Graves' disease (GD) should be simple. Stop the immune system from targeting the TSH receptor and the disease is cured. Unfortunately this is not yet feasible in most young people and GD is not a trivial condition for those affected. There are significant advantages and disadvantages of all current treatments with no easy way forwards for many and the family's decisions will reflect their perceptions of medical, radiation and surgical risk. The fact that two of the three standard treatments remove the thyroid gland (radioiodine ablation or total thyroidectomy) underlines the fact that what is simple in theory is not so simple in clinical practice.

Where are we in 2019?

1. **Anti-thyroid drug (ATD).** There is no data from clinical trials in the young to show that a block and replace (BR) ATD regimen has advantages over dose titration (DT). However larger doses of ATD will render the patient euthyroid more quickly and there are clinical scenarios where BR is useful. Longer term 'low dose' ATD is an attractive option for some families but how should we manage the small risk of agranulocytosis in those on anti-thyroid drug for several years? Perhaps not the best choice for those young people intent on travelling the world.
2. **Surgery (total thyroidectomy)** is a useful treatment in patients who fail to tolerate ATD or who relapse following an ATD course. Forging good links with an appropriately skilled and experienced surgical team is important and the nature of the discussions about surgical risk will impact on patient and family choice. Small risk of voice-change even in the best hands.
3. **Radio-iodine.** A key component of radioiodine treatment is parent and adolescent understanding of relative risk and how they manage associated uncertainty. What are the underlying reasons for the different 'national' approaches to this treatment modality? Theoretical risk of harm due to exposure to ionising radiation is increased in those young people who are still growing and developing.

New treatment strategies for GD are needed and an evolving clinical experience with immune modulation is heralding the start of a new era in Graves' disease research and management.

MTE 8

Management of neonatal hypoglycaemia

Klaus Mohnike

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Transition from intrauterine to extrauterine life is a vulnerable time and needs special attention by health professionals. Although only a small group of infants are at-risk for transitory, recurrent or permanent hypoglycemia prompt diagnosis and effective treatment had to avoid permanent brain injury. Neonatologists are aware of hypoglycemia in premature as well as in small for gestational age infants, however lower limits of blood glucose are often debated with endocrinologists and metabolic experts. Persistent hypoglycemia are mainly due to rare genetic disorders, resulting from a defect of insulin secretion of insulin, adrenal or pituitary insufficiency or defects in the metabolism of carbohydrates, proteins or lipids. Hypoglycaemia due to Congenital Hyperinsulinism (CHI) is of particular importance due to missing alternative energy sources. Insulin suppresses glucose production degradation of lipids and ketone bodies. CHI is a heterogeneous condition with variability in presentation, investigation and treatment. Histologically three types had been differentiated: focal, diffuse and atypical. Up to now, only focal-type CHI can be permanently cured by focus removal. Focal-type CHI is characterized by paternal inherited mutation of ABCC8 or KCNJ11 mutations. Therefore mutation analysis of both components of sulfonylurea channel gene is considered standard of care (soc). Localization diagnosis is recommended in all cases with mutation-positive results. In 2003 Otonkoski et al. described [18F]F-DOPA-PET as an accurate method to detect pancreatic hyperfunctioning focal area. Further modifications using hybrid technology of [18F]F-DOPA-PET-CT were developed and a high sensitivity had been described by expert centers. In these infants curative lesionectomy have improved clinical management significantly. In contrast, in diffuse and atypical CHI many uncertainties remain. Remarkable progress has been made in the management of CHI led to a considerable reduction of the frequency of subtotal pancreatectomy. The understanding of the pathogenesis of CHI led to a personalized management. Up to now, soc consists of frequent feeding, dietary management, diazoxide and somatostatin analogues. In addition, the development and authorisation of orphan medicines for rare diseases had been facilitated and industry-driven clinical studies with a variety of substances had been initiated.

How Do I

How Do I ... Session 1

HDI 1.1

Management of Subclinical Hypothyroidism

Mariacarolina Salerno

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Subclinical hypothyroidism (SH) is a biochemical condition defined by increased TSH serum concentration above the upper limit of the reference range associated with normal concentrations of T4 and Free T4. Depending on the degree of TSH elevation SH can be defined mild for TSH values between 4.5-10 mIU/l and severe for TSH levels >10 mIU/l.

The major cause of SH is chronic autoimmune thyroiditis, other causes are persistent neonatal hyperthyrotropinemia, TSH receptor gene mutations, genetic syndromes (Down, Turner, Williams, PHP), Iodine deficiency and excess, drugs (antiepileptic drugs, IFN- α), exposure to ionizing radiation (therapeutic/environmental), obesity and finally SH can be defined as idiopathic when no clear causes can be identified.

SH in children is often a benign and remitting condition. The risk of progression to overt hypothyroidism depends on the underlying cause being autoimmune SH associated with an increased risk of progression to overt hypothyroidism as compared to non-autoimmune SH.

The major concern regarding SH is to establish whether this condition should always be considered an expression of mild thyroid dysfunction. Growth and neurocognitive outcome in children do not appear to be affected by SH, however recent data suggest that mild SH may be associated with subtle pro-atherogenic abnormalities.

The benefits of levothyroxine therapy are far from clear, therefore the optimum management of children with SH remains a matter of debate and depends on the etiology and degree of TSH elevation and should be individually tailored.

Aim of this talk is to give an overview of current evidences on diagnosis and outcomes of mild SH in children and adolescents and to discuss the therapeutic options.

HDI1.2

Abstract not available

HDI1.3

Management of Insulin Resistance in Children

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Nowadays, after decades of continuously rising rates of paediatric obesity across the world, insulin resistance (IR) in children and adolescents has become a prominent health issue.

Obesity is recognised to be the most prevalent pathological cause of IR. However, corticosteroids or growth hormone therapy, genetic diseases and physiological conditions, such as puberty and pregnancy, may affect insulin sensitivity (IS) lifelong.

Early identification of IR and intervention during childhood, designed to reduce the metabolic risk in youth, are important health care issues and could influence future morbidity and mortality, as well as improve the quality of life.

The first approach to IR in children consists of lifestyle interventions (nutritional education, physical activity). These recommendations are often difficult to achieve, especially for adolescents, therefore, there is usually a lack of successful outcomes.

A pharmacological intervention in obese children may be needed in some cases, with the aim to improve the effects of these primary prevention interventions. Metformin seems to be safe and presents evident positive effects on insulin sensitivity, but long-term and consistent data are still missing to establish its role in the paediatric population and the possible effectiveness of other emergent treatments such as glucagon-like peptide-1 (GLP-1) analogues, dipeptidylpeptidase-4 (DPP-4) inhibitors, dual inhibitors of SGLT1 and SGLT2 and weight loss drugs.

Currently, there are some novel points of interest for researchers in this field, such as association between IR and sleep disturbances, hyperuricemia, adipocytokines, microRNAs, gut microbiota, as well as the possibility to use these associations in order to better understand the pathogenesis of IR.

Despite plenty of currently available information on IR in children and adolescents, there are still uncertainties regarding definition, prevention, management and treatment of IR in children.

How Do I ... Session 2

HDI 2.1

How do I.... manage micropenis in a child

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Micropenis is defined as a penile length less than 2.5 SD below the mean value for a given age (eg, <2.5 cm at term). Nowadays, it should be also diagnosed *in utero* by sonography. The incidence of micropenis has been reported as 1.5/10.000 male infants in USA, 5/1.442 in France and 18/2710 in Brazil, suggesting geographical differences or different assessment. Micropenis represents a

clinical sign, that may be part of various clinical conditions, such as hypogonadotropic hypogonadism, multiple pituitary hormone deficiencies, hypergonadotropic hypogonadism, defects in testosterone synthesis or action, and genetic or chromosomal syndromes. Iatrogenic causes (endocrine disrupters) may be involved. In some boys, the cause cannot be identified. Thus, accurate clinical and laboratory investigations are mandatory. Measurement with a ruler and comparison with available reference data permits the diagnosis. Ultrasound assessment of penis length may be an option mainly in perinatal period to obtain more accurate evaluation. Management should be performed by experienced multidisciplinary team to reach a definite diagnosis, to give an appropriate counseling and to optimize the care. Assessment of hormonal parameters of reproductive axis during the mini-puberty period and the availability of new genetic technologies may permit early etiology individuation and more rationale treatment planning. Irrespective of the underlying cause, a short course of testosterone may be tried in boys with micropenis to assess the response to androgens. Topical dihydrotestosterone gel is effective in young boys with 5alpha-reductase 2 deficiency. Infants with hypogonadotropic hypogonadism should be managed by recombinant human gonadotropins; growth hormone deficiency must be managed by appropriate hormonal therapy. Good self-body image and satisfactory sexual intercourses from adolescence onward are goals of treatment. Psychological counseling also for parents is advisable.

HDI 2.2

How do I diagnose growth hormone insensitivity

Marie-Jose Walenkamp

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Classical growth hormone insensitivity (GHI) is caused by a defect of the growth hormone receptor and is characterized by severe postnatal growth failure, craniofacial disproportion, IGF-I deficiency and normal or elevated levels of growth hormone. This is a rare condition. With the development of new genetic techniques during the last two decades other monogenetic defects resulting in milder forms of GHI have been identified. These include genes involved in the GH-IGF-I axis: *STAT5B*, *IGF-I*, *IGF1R*, *IGFALS* and *PAPPA2*. These defects present with a variable phenotype and biochemical profile and are likely to be more prevalent than the classical severe form of GHI. With the increasing availability of genetic investigations it is a challenge for the clinician to identify patients with short stature that should be analysed for further genetic analysis of the GH-IGF-I axis. Clinical scores have been developed to help the clinician in this diagnostic process. Recently a score for *IGF1R* analysis was proposed, including birth weight and/or length < -1 SDS, height at presentation < -2.5 SDS, head circumference < -2 SDS and IGF-I level > 0 SDS. If a patient meets at least three criteria *IGF1R* analysis is recommended. In this session the clinical and biochemical features of nonclassical causes of GHI will be discussed and diagnostic strategies will be proposed.

HDI2.3

Management of an asymptomatic child with T1D and transglutaminase positivity

Elke Frohlich-Reiterer

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The association between type 1 diabetes (T1D) and other autoimmune diseases is well known.

The prevalence of celiac disease (CD) ranges from 1% to 10% among children and adolescents with T1D.

The risk of associated CD is inversely and independently associated with age at diagnosis, with the greatest risk in those diagnosed with T1D before the age of 5 years. Classical symptoms of CD as poor growth, weight loss, gastrointestinal symptoms, abdominal pain and anaemia are rare in children with T1D, as most of the children with T1D and CD are asymptomatic. Therefore, international guidelines recommend screening for CD in children with T1D. Screening is based on IgA antibodies (tissue transglutaminase (tTG-A) and/or endomysial (EmA). As IgA deficiency is more common in people with T1D and those with CD, IgA deficiency has to be excluded. If the child is IgA deficient, IgG-specific antibody tests (tTG or EMA IgG, or both) need to be used for screening.

Recent guidelines recommend testing for HLA-DQ2 and HLA-DQ8 because CD is unlikely if both haplotypes are negative. As a high proportion of patients with T1D carry these risk alleles, HLA testing as first line screening test for CD is not practical.

If CD specific antibodies are positive, a small bowel biopsy is needed to confirm the diagnosis by demonstrating subtotal villus atrophy using Marsh classification.

tTG positivity at the time of diabetes onset may also be transient emphasizing the need of retesting of CD specific antibodies and the need of duodenal biopsy to verify diagnosis.

A gluten-free diet normalizes the bowel mucosa and leads to normalization of antibodies. The aim of the gluten-free diet also includes the reduction of gastrointestinal malignancy and conditions associated with malabsorption as iron deficiency and osteoporosis. Furthermore, recent studies show that patients with T1D and CD may have a higher risk for retinopathy and non-adherence to gluten-free diet may increase the risk for albuminuria. Children and adolescents with T1D, with poor adherence to a gluten-free diet, may also have worse glycemic control and reduced quality of life.

Screening for CD in children and adolescents with T1D is recommended at time of diabetes onset and at 2 and 5 years thereafter. More frequent measurements are indicated if the patients has clinical symptoms or a first-degree relative with CD.

Novel Advances

NA1

Abstract not available

NA2

Genomic imprinting analysis in clinical practice

Deborah Mackay

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Genomic imprints in humans are epigenetic marks inscribed upon our genomes from the earliest stages of our development, forming a permanent memory of our parental origin. Approximately 1% of human genes are imprinted, with expression that is permanently restricted to either the paternal or the maternal DNA. Genetic or epigenetic errors of imprinting cause a range of imprinting disorders, each with distinctive effects upon growth, development, metabolism and behaviour.

This talk will show how a clinician can approach diagnosis for a child with a suspected imprinting disorder, using as an example the growth restriction disorder Silver-Russell syndrome (SRS). The molecular diagnosis of imprinting disorders is complex and there is a need for close collaboration between the clinician and the genetics laboratory. I will illustrate the sequential approach that is required for molecular investigation to achieve diagnosis for an imprinting disorder, and in the process, I will explore their genetic and epigenetic causes, their clinical heterogeneity, and the relationships between (epi)genotype, presentation, and prognosis.

CON 1.2

Does obesity need tertiary care provision? – Against!

Wieland Kiess

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In view of the high prevalence of obesity in childhood and adolescence treatments of obesity in young ages represent a major burden to the health care systems around the world. However, still treatments are ineffective largely, and little is being done to organize effective prevention and to enhance societal understanding of the complex etiology of the disease. In more developed and industrialized countries, and that is in all of Europe and in North America as well as in Australia and New Zealand, the majority of children and adolescents who are obese come from less educated and less affluent families. Low income and lower education of the families as well as polygenic traits are the major contributors for an individual child to develop obesity at a young age. In addition, societal conditions such as availability of cheap sugar-rich nutrition and sugar-containing beverages as well as lack of walkability in neighborhoods all contribute to the obesity epidemic. It is society not medicine who needs to understand the real causes of the majority of the obesity problem. It is only a small minority of children with obesity that suffer from obesity syndromes or carry monogenic traits such as MC4R defects, leptin receptor defects, POMC variants or leptin deficiency. Only these individuals need tertiary care facilities with comprehensive genetic testing, centers for rare diseases and facilities for clinical trials. It is being postulated, that extensive screening strategies involving public health facilities, primary care physicians and school doctors should be able to identify these few patients with non-primary obesity who eventually do need tertiary care facilities. Prevention and societal change on the other hand should be brought about through research, education and mass media based information to the general public. Herewith, not tertiary care but primary scientific work is needed. Flooding expensive tertiary care facilities with millions of obese children who suffer from societies' ill conditions and bad environments cannot be afforded and does not help to contain the childhood obesity epidemic. Most importantly, little effects are being seen when treatment concepts even involving tertiary centers are put forward.

Controversies

Does obesity need tertiary care provision?

CON 1.1

Abstract not available

Young Investigators

YI1.1

Abstract not available

YI1.2**Early life events and postnatal effects from infancy to childhood**

Valentina Chiavaroli

Pescara Italy

Early life events can profoundly affect an individual's metabolic phenotype, inducing adaptive responses that may be protective *in utero* but potentially disadvantageous for long-term health. Indeed, environmental cues during sensitive windows of development may result in altered growth and lead to an increased risk of cardiovascular and metabolic alterations later in life. In this talk, I will discuss several models of exposure to early life events, which were the topic of my 2015 ESPE Long-term Research Fellowship.

such centralization includes high thresholds concerning infrastructure not achievable in all health systems. Alternatives such as multicenter-based networks for reference assessments should be considered to assure high standards of treatment quality. Even though overall survival rates are high (92%), recurrences and progressions are frequent. Irradiation has proven effective in reducing recurrences and progression. Proton beam therapy – available on a wider range in the near future – will help to avoid radiooncological side effects. Anatomical involvement and/or surgical lesions of posterior hypothalamic areas can result in serious quality of life compromising sequelae such as hypothalamic obesity, psychopathological symptoms, and/or cognitive problems. Novel insights into neuropsychological sequelae after CP should be the basis for the development of future therapeutic neuropsychological interventions. It is crucial that CP should be managed as a frequently chronic disease, providing ongoing care of pediatric and adult patients' clinical and quality of life consequences by experienced multidisciplinary teams.

Working Groups

Abstracts not available

Endo-ERN Session

ERN1.1**Life Long Management of Childhood Craniopharyngioma**

Hermann L. Müller

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Craniopharyngiomas (CP) are rare, partly cystic and calcified embryonic malformations of the sellar/parasellar region with low histological grade (WHO Ia). A bimodal age distribution has been shown, with peak incidence rates in childhood-onset at 5–14 yr and adult-onset CP at 50–74 yr. Clinical manifestations are related to hypothalamic/pituitary deficiencies, visual impairment, and increased intracranial pressure. Recent insight in molecular pathogenesis of CP opens new perspectives on targeted therapy. Further research to elucidate pathogenic mechanisms and hopefully prevent hypothalamic involvement of CP is warranted. If the tumor is favorably localized, therapy of choice is complete resection, with care taken to preserve optical and hypothalamic functions. In patients with unfavorable tumor localization (i.e., hypothalamic involvement), recommended therapy is limited hypothalamus-sparing surgical strategy followed by local irradiation. Surgical treatment strategies should be based on a multidisciplinary approach involving experienced teams. Centralizing treatment of CP in experienced "centres of excellence" is recommended. However,

Free Communications

Diabetes and Insulin Session 1

FC1.1**Insulin Resistance Leads to Mitochondrial Dysfunction in Hepatocyte**

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Background: Insulin resistance in obesity and type 2 diabetes is associated with abnormalities in mitochondrial oxidative phosphorylation in skeletal muscle. Whether mitochondrial function changes in hepatocytes with hereditary insulin resistance is not clear. Type A Insulin Resistance Syndrome (TAIRS) is a rare disorder characterized by severe insulin resistance, a condition in which the body's tissues and organs do not respond properly to the hormone insulin. TAIRS is often caused by mutations in the *INSR* gene, leading to insulin receptor dysfunction.

Objective and Methods: To define the causal relationship between hereditary insulin resistance and mitochondrial dysfunction, we used Crispr/cas9 technology to precisely edit the *INSR* gene in hepatocellular carcinoma (HepG2) cells to construct a hereditary model of insulin resistance. Mitochondrial metabolism, oxidative respiratory chain and reactive oxygen species (ROS) levels were compared in wild type (*INSR*-WT) and mutant (*INSR*-MUT) HepG2 cell lines.

Results: Compared with the *INSR*-WT group, *INSR* gene mutation resulted in incomplete activation of downstream PI3K-Akt and MAPK-Erk signaling pathways and decreased cell glucose

uptake. Mitochondrial function was changed in the INSR-MUT group, and oxidative respiratory chain-related proteins (such as ND5, ATP8 and Cox2) were significantly increased, and ATP production was reduced. Mitochondrial ROS increase, exacerbating insulin resistance.

Conclusions: Insulin resistance caused by INSR gene mutation can lead to mitochondrial dysfunction in hepatocyte, abnormal oxidative respiratory chain and reduced energy production. In addition, increased ROS may aggravate insulin resistance.

Key words: Insulin resistance, INSR, Mitochondrial Dysfunction, Gene

FC1.2

Three New Genes (PTPRD, SYT9, and WFS1) related to Korean Maturity-onset Diabetes in the Young (MODY) Children Decrease Insulin Synthesis and Secretion in Human Pancreatic Beta Cells

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Background: MODY includes a very heterogenous group of monogenic diabetes mellitus characterized by beta-islet cell dysfunction. We previously reported 3 new gene mutations of PTPRD, SYT9 and WFS1 in Korean MODY children (Horm Res Paediatr, 2015). We investigated whether the PTPRD, SYT9 and WFS1 mutation overexpression vectors affect insulin synthesis and secretion in human pancreatic beta cells. .

Materials & Methods: We used 1.4E7β cell lines for human pancreatic β-cells. PTPRD, SYT9 and WFS1 genes wild type (WT) vectors, mutation type (MUT) vectors, and siRNAs were transfected into the cells, and insulin secretion and cellular functions of insulin synthesis were examined.

Results: 1.4E7β cells were transfected with PTPRD, SYT9 and WFS1-WT vectors, -MT vectors, siRNA and a scramble siRNA as a negative control. PTPRD-WT, SYT9-WT and WFS1-WT were highly expressed in 1.4E7β cells. PTPRD-MUT, SYT9-MUT and WFS1-MUT were like normal control (1.4E7β cells without transfection). These 3 gene knockdowns by siRNAs confirmed a decrease in protein synthesis. Firstly, we evaluated changes in ATP/ADP ratio in PTPRD, SYT9 and WFS1-WT or MUT transfected 1.4E7β cells. When compared with normal control (1.4E7β cells without transfection), the increase in intracellular ATP after high glucose stimulation was nearly 290% in PTPRD-WT, SYT9-WT and WFS1-WT. However, PTPRD-MUT and WFS1-MUT inhibits glucose stimulated intracellular ATP. SYT9-MUT has no effect on ATP/ADP ratio increased by glucose. Secondarily, we examined changes in the surface expression levels of Kir6.2 which is closely related to insulin secretion using surface biotinylation/streptavidin purification and subsequent. The increase in Kir6.2 surface (s-Kir6.2) was increased by stimulation of glucose in PTPRD-WT, SYT9-WT and WFS1-WT. However, PTPRD-MUT, SYT9-MUT and WFS1-MUT inhibits glucose stimulated s-Kir6.2 expression. Among them, PTPRD-MUT highly reduced s-Kir6.2 expression

by glucose in 1.4E7β cells. Thirdly, Metabolic disturbances like a hyperglycemia in a certain type of diabetes mellitus etc induce endoplasmic reticulum (ER) stress which represents decline in synthesis of insulin in pancreatic β-cells. The effect of mutations of PTPRD, SYT9 and WFS1 on glucose induced ER stress was performed. Glucose treatment highly increased ER stress markers (BiP, CHOP and pPERK) in PTPRD-WT, SYT(-WT and WFS1-WT. PTPRD-MUT highly inhibits glucose induced all 3 stress markers in 1.4E7β cells. Interestingly, SYT9-MUT highly inhibits only glucose induced BiP expression. WFS1-MUT moderately inhibits glucose induced BiP and CHOP expression in 1.4E7β cells.

Conclusion: Our results confirmed that single-point mutations of PTPRD, SYT9 and WFS1 showed impaired glucose-induced insulin release and synthesis in human pancreatic β-cells.

FC1.3

Next Generation Sequencing in Greek MODY patients increases diagnostic accuracy and reveals a high percentage of MODY12 cases

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Introduction: Maturity Onset Diabetes of the Young (MODY) constitutes a genetically and clinically heterogeneous type of Monogenic Diabetes (MD), characterized by early onset of hyperglycemia, autosomal dominant inheritance and defect in β-cell insulin secretion. To date, 14 different MODY subtypes have been reported, each one with a distinct genetic etiology.

Materials and Methods: We designed a NGS TGP of seven MODY genes (GCK, HNF1A, HNF4A, HNF1B, INS, ABCC8 and KCNJ11) and screened 50 patients fulfilling MODY criteria. The patients, with no pathogenic variant, were tested by Multiplex Ligation-dependent Probe Amplification (MLPA) for CNVs. All detected pathogenic variants were verified by Sanger sequencing.

Results: Fifteen pathogenic heterozygous variants were detected in sixteen unrelated patients (diagnosis rate 32%) of which 14% were ABCC8, 8% GCK, 6% HNF1A, 2% HNF4A and 4% r HNF1B gene variants. One digenic case (GCK and ABCC8) was detected. Five variants were novel (GCK; p.Cys371X, HNF1A; p.Asn402Tyr, HNF4A; p.Glu285Lys and ABCC8; p.Met1514Thr and p.Ser1386Phe). Two *de novo* heterozygous deletions of the whole HNF1B gene were detected in two patients by MLPA, increasing the diagnosis rate of this work to 36%. The ABCC8 MODY patients (14%) presented with a wide spectrum of clinical and biochemical characteristics: fasting blood glucose ranging from 103 to 365mg/dl (5.7-20.3mmol/l), HbA1c 6.2% to 11.9% (44.3 - 107mmol/mol), age of onset of diabetes from 9yrs to 42 yrs, BMI from 17.2 kg/m² to 27.7 kg/m² and birth weight from 2800gr to 4100gr. Similar phenotypic heterogeneity has been described in the ABCC8 (MODY12) patients reported in the literature to date

Conclusions The application of NGS methodology in MD diagnosis provide rapid results, is cost effective compared to Sanger sequencing and increases diagnostic accuracy. In this work MODY 12 represented 14% of the patients studied, although it is considered rare (<1%) in the literature. This finding can be attributed to the high throughput methodology of NGS, rendering sequencing the ABCC8 gene (39 exons) feasible compared to Sanger sequencing. The phenotypic characteristics of the patients carrying ABCC8 variants, exhibit genetic heterogeneity, ranging from a mild phenotype, similar to the mild GCK phenotype, to a more severe phenotype, similar to that of HNF1A and HNF4A defects. Molecular genetic diagnosis of the MODY subtype is of outmost importance for clinical diagnosis, disease progression prognosis and family counseling. Furthermore, it specifies pharmacologic treatment, since different MODY subtypes require different therapeutic approaches, constituting an example of personalized medicine.

FC1.4

Abstract withdrawn

FC1.5

FADES: A birth cohort to understand the mechanisms underlying accelerated onset of autoimmunity in children with Down's syndrome

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Background and Aims: Children with Down's syndrome (DS) are at increased risk of autoimmune conditions including type 1 diabetes (T1D), coeliac and thyroid disease. We previously examined the clinical and immunogenetic characteristics of these conditions in children with DS. An earlier age-of-onset of diabetes was observed compared with children with T1D from the general population despite having decreased frequencies of the established genetic susceptibility factors for T1D. In order to understand the mechanisms underlying accelerated onset of autoimmune diabetes and other forms of autoimmunity in children with DS, we initiated a UK wide birth cohort FADES (Feeding and Autoimmunity in Down's syndrome Evaluation study) to examine the longitudinal development of factors related to autoimmunity in these children.

Material and Methods: Infants with DS were recruited under 8 months of age. Parents completed medical and feeding questionnaires at initiation, 6 and 12 months and annually thereafter. Questionnaires included information about medical conditions, infections, antibiotic use and early feeding weaning. Mouth brushes were collected for DNA. Longitudinal urine samples were collected for Urinary C-Peptide Creatinine Ratio (UCPCR) and metabolomics, stool samples for gut microbiome and blood samples for autoantibodies. HLA susceptibility was analysed by PCR-SSP, and UCPCR by electrochemiluminescence. Serum samples were analysed for autoantibodies by radioimmunoassay.

Results: Recruitment is ongoing. To date, 95 UK infants with DS (Male n=49) have been consented; mean age at recruitment 18.4 weeks (S.D.10 weeks). Initial questionnaires have been completed by 88% of participants and at one year old by 66%; 64 participants are now over 2 years of age. Initial DNA, urine, stool and blood samples have been obtained from 77%. Of 60 children tested to date, 37% have at least one of the high risk HLA genotypes DR4-DQ8 or DR3-DQ2 for T1D. No participant has been diagnosed with T1D and this is confirmed by Urinary C peptide levels in the normal range at 1 year. Insulin autoantibody screening is ongoing; 43 participants were negative at age 2 years. Two children have developed thyroid abnormalities but are negative for thyroid peroxidase antibodies. One child, homozygous for HLA DR3-DQ2 was positive for autoantibodies to tissue transglutaminase at age 1 year consistent with a diagnosis of coeliac disease by ESPGHAN guidelines but was not diagnosed clinically until age 4.

Conclusions: FADES is the first and largest DS birth cohort to study the longitudinal development of the factors associated with autoimmunity in this high risk population.

FC1.6

A novel biochemical marker, fatty acid-binding protein 4, in diabetic ketoacidosis in children

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Introduction: Diabetic ketoacidosis (DKA) is the most common cause of hospitalization, cerebral edema, and death among children with type 1 diabetes (T1D). Fatty acid-binding protein 4 (FABP4 or aP2) is one of the most abundant proteins in adipocytes and has been shown to be actively secreted from adipocytes. Circulating FABP4 is regulated by fasting- and lipolysis-related signals and contributes to hyperglycemia by promoting hepatic gluconeogenesis and interfering with peripheral insulin action, implicated in the pathology of many metabolic diseases, including diabetes in humans. Therefore, FABP4 appears as an active adipokine that

counter-regulates insulin action and plays crucial hormonal functions in systemic glucose metabolism.

Aims: To determine the correlation between FABP4 and new-onset T1D and to differentiate between DKA and non-DKA situations.

Methods: Clinical and laboratory data were prospectively collected from children who presented with new-onset T1D during the year 2017 from one tertiary medical center. In addition to chemistry and blood gases, FABP4 and free fatty acids (FFA) were collected upon presentation and 48-72 hours after initiation of insulin treatment. The patients were divided to two groups – DKA and non-DKA.

Results: Out of 32 children, with mean age of 9.3 ± 3.5 years, 17 (53%) were male and 13 (40%) presented with DKA. The mean FABP4 level was higher amongst the DKA group, 12.1 ng/ml as opposed to 8.7 ng/ml in the non-DKA group. The delta between the first FABP4 and the second sample after insulin treatment was almost twice in the DKA group compared to the non-DKA group (8.1 vs. 4.5, p-value=0.03). There was a correlation between the FABP4 level and the FFA level in both groups.

Conclusions: We describe a novel biochemical marker, FABP4, which is increased in lipolysis and particularly in DKA. This finding can shed light on the mechanisms involved in DKA.

phosphate homeostasis and rickets in children with XLH. Here, we report final data from this Phase 2 Study CL201 (NCT02163577).

Fifty-two children with XLH (5-12 years old, Tanner ≤ 2) were randomized 1:1 to receive subcutaneous burosomab every 2 (Q2W) or 4 (Q4W) weeks for 64 weeks. All subjects entered the long-term extension at Week 64, in which the Q4W group switched to Q2W, and completed the study (≥ 160 Weeks).

After Q4W switched to Q2W at Week 64, results between groups were similar by Week 88 and combined for the Week 160 analysis. Nearly all (50/52, 96%) subjects achieved a normal serum phosphorus level (3.2-6.1 mg/dL) by Week 160. Decreases in total Rickets Severity Score at Week 64, were maintained, with an LS mean \pm SE change from baseline to Week 160 of -0.9 ± 0.1 ($p < 0.0001$) in 42 subjects with open growth plates (11 had closed growth plates at distal femur and proximal tibia). Improvement in the Radiographic Global Impression of Change (RGI-C; N=42) global score observed at Week 88 ($+1.6 \pm 0.1$) was maintained at Week 160 ($+1.7 \pm 0.1$, $p < 0.0001$). RGI-C lower limb deformity score continued to improve (Week 88: $+0.6 \pm 0.1$, $p < 0.0001$; Week 160: $+1.1 \pm 0.1$, $p < 0.0001$). Improvements in height Z-score at Week 160 (LS mean increase \pm SE: Q2W $+0.35 \pm 0.08$, Q4W \rightarrow Q2W $+0.19 \pm 0.09$) were almost doubled compared to Week 64 (Q2W $+0.20 \pm 0.05$, Q4W \rightarrow Q2W $+0.11 \pm 0.06$). Increases in 6-Minute Walk distance observed at Week 64 were maintained through Week 160. Sports/Physical functioning and Pain/Comfort scores significantly improved from below normal at baseline to within the normal range at Week 160 (both $p < 0.0001$). One subject had 2 AEs (fever/muscle pain and headache) classified as serious due to brief hospitalization; both resolved within a week. Other AEs were generally mild to moderate in severity. Change from baseline to Week 160 in nephrocalcinosis score was 0 in 39 subjects, +1 in 9 subjects, +2 in 1 subject, and -1 in 3 subjects. No noteworthy changes in serum calcium or PTH occurred. No subject developed hyperphosphatemia.

Long-term burosomab in children with XLH was associated with continued improvement in rickets, leg deformities, growth, and pain scores, as well as sustained improvement in mobility and normalization of phosphate homeostasis.

Bone, Growth Plate and Mineral Metabolism Session 1

FC2.1

Continued Improvement in Clinical Outcomes with Burosomab, a Fully Human Anti-FGF23 Monoclonal Antibody: Results from a 3-year, Phase 2, Clinical Trial in Children with X-Linked Hypophosphatemia (XLH)

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In children with XLH, excess FGF23 causes hypophosphatemia with consequent rickets, skeletal deformities, and impaired growth and mobility. We previously reported that burosomab improved

FC2.2

Benefits of Long-term Burosumab Persist in 11 Girls with X-Linked Hypophosphatemia (XLH) Who Transitioned into Adolescence during the Phase 2 CL201 Trial

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In children with XLH, excess FGF23 causes hypophosphatemia with consequent rickets, skeletal deformities, and impaired growth and mobility. We reported that burosumab improved phosphate homeostasis and rickets in children with XLH. Here, we present data on 11/52 subjects (all girls) who developed fused growth plates during the phase 2 study CL201 (NCT02163577).

In CL201, 52 subjects (Baseline: 5-12 years-old, Tanner ≤ 2) were randomized 1:1 to receive burosumab subcutaneously Q2W or Q4W for 64 weeks. All entered the long-term extension at Week 64, in which the Q4W group switched to Q2W, and completed ≥160 weeks.

Among the 52 subjects, 11 girls developed fused growth plates at the distal femur and proximal tibia (mean age: baseline 9.8 years, Week 160 13.3 years; mean Tanner stage: baseline 1.5, Week 160 3.4). Serum phosphorus levels for these 11 girls were maintained near the lower limit of normal (3.2 mg/dL) throughout the study. For the 10/11 girls whose last visit with open growth plates was Week 88, mean total Rickets Severity Score (RSS) decreased from 2.1 at baseline to 0.4 at Week 88, and the mean Week 88 Radiographic Global Impression of Change (RGI-C) was +2.3, both indicating improved rickets. Similarly, for the 1 girl whose last visit with open growth plates was Week 64, RSS decreased to 0 from 1.5 at baseline, with a Week 64 RGI-C of +2.7. In these 11 girls, LS mean RGI-C lower limb deformity score improved: +0.4 at Week 64 and +1.1 at Week 160. Standing height Z-score improved from a mean (SD) of 1.7 (0.9) at baseline to -1.5 (1.0) at Week 160. Mean sports/physical functioning and pain/comfort scores improved from below population norms at baseline to within population norms at Week 160. All adverse events (AEs) in these girls were mild or moderate in severity and most related-AEs were injection site reactions. At Week 160, nephrocalcinosis scores were unchanged from baseline in 10 subjects and 1-point lower in 1 subject. No clinically meaningful changes in serum calcium or PTH occurred. None of these girls developed hyperphosphatemia.

Benefits persisted with long-term burosumab in these 11 girls with XLH who developed fused growth plates during this study, including sustained improvements in phosphate metabolism, resolving rickets (assessed with open growth plates), better physical functioning, and less pain. These patients also showed continued improvement in leg deformities and growth.

FC2.3

Higher Dose Of Burosumab is Neededfor Treatment of Children with Severe Forms of X-Linked Hypophosphatemia

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Background/aim: X-linked hypophosphatemia (XLH) is a rare disease caused by mutations in PHEX, leading to elevated FGF23 levels, hypophosphatemia and chronic renal phosphate wasting. Burosumab is a monoclonal antibody against anti-FGF23, which has been recently approved for treatment of XLH. Beyond clinical trials, little is known about its efficacy/safety in clinical practice which is the aim of study.

Patients/methods: 45 children with XLH were switched from conventional therapy to burosumab (starting dose 0.4 mg/kg), on the basis of following indications: non-responder to conventional therapy (persistence of leg deformities and elevated levels of alkaline phosphatase, need for orthopaedic surgery, presence of neurological, dental, hearing complications, secondary hyperparathyroidism, height <-2SDS treated or not with rhGH); intolerance to conventional therapy (nephrocalcinosis), late diagnosis (>8 years). Serum phosphate level (sP) was checked before starting burosumab (M0) and monitored every 2 weeks for dose adjustment (target sP >1.2 mmol/l). Other parameters (ALP, 1,25(OH)₂D, PTH, TmP/eGFR, CaU/CrU, side effects) were checked at M0, thereafter at 3-6-9 months of treatment (M3-M6-M9). Severe and non-severe forms of XLH were defined by >2 and ≤2 complications.

Results: 45 children (29 girls/16 boys, mean age 9.7±3.7 years) were treated with conventional therapy for 7.3±3.9 years before starting burosumab. 28 patients completed 9 months of burosumab treatment. Upon burosumab, levels of sP, TmP/eGFR, 1,25(OH)₂D increased significantly (sP 0.7±0.1→1.2±0.2 1.2±0.2→1.2±0.1 mmol/l; TmP/eGFR 0.6±1.1→1.1±0.2 1.1±0.2→1.1±0.1; 1,25(OH)₂D 26.2±15.7→73.8±22.7→88.4±39.9→82.5±19.9 pg/ml, M0-M3-M6-M9, respectively, p for trend=0.000) and ALP decreased significantly (414±153 339±141 339±146 313±148 UI/l, M0-M3-M6-M9, respectively, p for trend=0.036). At M9, the average dose of burosumab was 1.4±0.5 mg/kg (47±25 mg); 39% (n=9) of patients did not achieve target sP level. At M9, 32% (n=9) of subjects received the maximal dose of burosumab (2.0 mg/kg or 90 mg), yet having low sP level. Children with the severe form of XLH needed higher final dose of burosumab compared with patients having the non-severe form (1.4±0.5 vs 1.1±0.5 mg/kg, 53±27 vs 34±20 mg, respectively, p=0.068 and 0.017, respectively). No severe adverse events were noticed, the most frequent side effect being redness at sites of injection, muscular/bone/abdominal pain.

Conclusion: Treatment with burosumab restores phosphate renal reabsorption, increases sP and endogenous 1,25(OH)₂D synthesis. The dose of burosumab should be adjusted to the severity of the disease.

FC2.4

New imaging approaches to the quantification of musculoskeletal alterations in X-linked hypophosphatemic rickets (XLH)

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Background: X-linked hypophosphatemia (XLH) is a rare genetic disorder of phosphate metabolism caused by mutations in the PHEX gene. XLH patients exhibit short stature and skeletal

deformities, which are caused by defective bone mineralization site leading to increased porosity and decreased matrix stiffness. Bone mineral density measurements have been shown to be insensitive to the cumulative bone alterations. The velocity of the first arriving signal (vFAS) measured in bi-directional axial transmission (BDAT) is determined by cortical thickness, cortical porosity and matrix stiffness. Therefore, we hypothesized that ultrasound may be a potential alternative to quantify the onset and severity of the disease.

Methods: Following study approval by institutional review and written informed consent, we performed quantitative bone ultrasound in children, adolescents and young adults with XLH (N=8) and healthy controls (N = 13). A sub-group majority of patients (n = 4) and controls (n = 4) also underwent high-resolution peripheral quantitative computed tomography (HR-pQCT) of the ultra-distal radius and tibia. Bone ultrasound was performed at the distal radius and the central distal tibia according to a structured examination protocol, using a certified BDAT system (Althais, France) equipped with a 1.2 MHz linear transducer array with 2 x 5 transmit elements and a central 24 element receiver array. The velocity of the first arriving signal (vFAS) was determined from 100 measurement cycles at each measurement location. HR-pQCT images were reviewed by a board-certified radiologist, cortical and trabecular parameters were evaluated using the manufacturer's software.

Results: BDAT measurements were conducted successfully in all study participants. The velocity of the first arriving signal (V_{FAS}) in BDAT ultrasound was significantly lower in XLH patients compared to healthy controls: In the radius, mean V_{FAS} of XLH patients and controls was 3553 ± 196 and 3873 ± 143 m/s, respectively (-8.3 %; p < 0.001). In the tibia, it was 3531 ± 156 and 3757 ± 119 m/s, respectively (-6.0 %; p = 0.019). HR-pQCT revealed a slightly increased trabecular thickness in XLH patients (XLH: 0.07 mm, controls: 0.06 mm, p = 0.02).

Discussion and Conclusion: These preliminary results suggest that sound velocity is a suitable indicator for XLH associated bone alterations. Regular monitoring of XLH patients by a radiation-free technology such as BDAT might provide valuable information on bone quality and contribute to the optimization of treatment. Further studies are needed to establish this affordable and time efficient method in the XLH patient cohort.

FC2.5**Age And Gender-Specific Reference Data For High-Resolution Magnetic Resonance Based Musculoskeletal Parameters In Healthy Children And Young People**

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Background: The need to understand the relationship between bone, muscle, and fat within the bone-muscle unit has recently gained great prominence. Although high resolution (HR) MRI is a non-invasive imaging modality that can provide this information, there is limited expertise in children and young people.

Objectives: To establish MRI-based normative data for bone, bone marrow adiposity and muscle adiposity in children and young people.

Methods: 3T MRI of distal femur and proximal tibia was performed in healthy subjects aged between 8-29 years to assess trabecular microarchitecture (both sites), cortical bone geometry (femur); muscle area and adiposity (muscle fat fraction, MFF) was assessed at distal femur and ¹H-MRS of lumbar spine (L3) was performed to assess bone marrow adiposity (bone marrow fat fraction, BMFF).

Results: Of the 140 participants, 60 (M:F, 32:28) with a median age of 13yrs (range, 8.1, 23.8) for males and 13.6yrs (8.4, 22.3) for females were scanned at proximal tibia; 80 participants (M: F, 46:34) with a median age of 14yrs (8, 29) and 17.6yrs (9.3, 28) for males and females, respectively, were scanned at the femur. No sex differences were observed in trabecular microarchitecture but there was an inverse association of apparent trabecular bone volume fraction (app BV/TV) with age at tibia in both sexes ($r=-0.58$ $p<0.005$) and at femur in females ($r=-0.37$, $p=0.03$). Compared to the femur, the tibial scans revealed a higher appBV/TV (0.595 vs 0.550, $p<0.005$), higher trabecular numbers (appTbN) (1.988 vs 1.853mm⁻¹, $p<0.005$) and lower trabecular separation (appTbSp)(0.200 vs 0.239mm, $p<0.005$). Cortical area and endosteal and periosteal circumferences showed a positive association to age ($r=0.49$, $p<0.005$). Although cortical parameters tended to be higher in males than females, the difference did not reach statistical significance. Median BMFF was similar in females and males at 22.3% (9.4, 41.5) and 25.8% (4, 47.1) respectively (NS). Muscle area showed a positive association with age ($r=0.76$ $p<0.005$) which persisted when adjusted for height ($b=0.39$, $p=0.001$). After accounting for age and height, BMFF showed an independent association with weight ($b=0.46$, $p=0.02$). MFF was 3.9% (0.6, 9.9) and 4.5% (0.5, 9.7) in males and females, respectively (NS).

Summary: In addition to providing further insight into the normal relationships between bone, fat, and muscle, these novel data also emphasize the place of MRI as a non-invasive tool for the integrated assessment of musculoskeletal health in the young person.

FC2.6**Validation of a new version of BoneXpert bone age in children with congenital adrenal hyperplasia (CAH), precocious puberty (PP), growth hormone deficiency (GHD), Turner syndrome (TS), and other short stature diagnoses**

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Background: The BoneXpert method for automated determination of bone age from hand X-rays is based on machine learning, so it lends itself naturally to be improved by adding more training data and using better learning algorithms. Currently, version 2 is running in 145 hospitals across Europe, and a new version 3 is rolled out in 2019.

Objective and Hypotheses: The aim was to validate version 3 against manual ratings in retrospective studies, for which the performance of the previous version of BoneXpert has already been published.

Method: The training set included 14036 public images from the 2017 RSNA Bone Age Challenge, 1642 images of normal Dutch and Californian children, and three studies from Tübingen collected 1976-2006: 6743 images of short stature (GHD, TS, Silver-Russell Syndrome, idiopathic short stature etc), 775 images of CAH, and 732 images of PP. The learning algorithm included more accurate and robust localisation of the bones, an extension of the bone age range down to new-borns, and adding of carpal and finger 2 and 4. We report the results as the cross-validated root mean square errors (RMSE) of the method relative to the original manual rating.

Results: The RMSE in short stature improved from 0.74 years for the current version to 0.64 years for version 3. For CAH, the RMSE improved from 0.67 to 0.57 years and for PP from 0.68 to 0.60 years. The overall improvement was from 0.72 to 0.63 years.

Conclusion: The accuracy of automated bone age rating is now so good, that the observed error relative to a single manual rating is dominated by the uncertainty of the manual rating. The standard deviation of manual ratings, when repeated by different observers, is 0.52-0.64 years in clinical routine, and the Tübingen raters are believed to lie at the lower end of this interval.

The observed RMSE thus tells more about the rater variability of the particular raters than uncertainty of the method. Therefore, we recommended that future validation studies compare the AI method to the average of three or more raters. This will reduce the error of the “reference”, and at the same time allow an estimate of the interrater variability. In the RSNA Challenge, a test set of 200 images was rated by six raters, and the new version obtains an RMSE of 0.45 years against the average. Automated bone age rating is now clearly better than a single manual rating.

Multi-System Endocrine Disorders

FC3.1

Germline-derived Gain-of-Function Variants of Gsa-coding GNAS Gene Identified in Nephrogenic Syndrome of Inappropriate Antidiuresis: The First report

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Background: The stimulatory G-protein α -subunit encoded by GNAS exons 1–13 (GNAS-Gsa) mediates signal transductions of multiple G-protein-coupled receptors including arginine vasopressin (AVP) receptor 2 (AVPR2). To date, various germline-derived loss-of-function variants of maternal and paternal origin have been found in pseudohypoparathyroidism type Ia and pseudopseudohypoparathyroidism respectively, and specific somatic gain-of-function (GOF) variants have been detected in McCune-Albright syndrome (MAS). However, no germline-derived GOF variant has been identified.

Methods: We performed whole exome sequencing (WES) in family-A and family-B with dominantly inherited nephrogenic syndrome of inappropriate antidiuresis (NSIAD), after excluding a GOF variant of AVPR2. We subsequently performed functional studies for identified variants.

Results: WES revealed p.(F68_G70del) and p.(M255V) of GNAS-Gsa as the candidate variants for NSIAD in family-A and family-B, respectively. Both variants were absent from public and in-house databases and, of genes with rare variants, GNAS-Gsa alone was involved in AVPR2-signaling and shared by the two families. Protein structural analyses revealed a GOF-compatible conformational property for p.M255V-Gsa, although such assessment was not possible for p.F68_G70del-Gsa. Luciferase reporter assays showed that both variants had constitutive activation functions which were significantly milder than those of MAS-specific Gsa variants. Model mice for p.F68_G70del-Gsa showed normal survivability and NSIAD-compatible phenotype, while those for p.M255V-Gsa exhibited severe failure to thrive. NSIAD was the sole clinically recognizable phenotype in the two families, while detailed clinical and laboratory studies in the GNAS-Gsa variant-positive subjects revealed subclinical hyperthyroidism in four subjects and hypocalciuria in a single subject.

Conclusions: This study shows for the first time that germline-derived GOF variants of GNAS-Gsa do exist and cause NSIAD as a novel Gsa-mediated genetic disease. It is likely that AVPR2-signaling is most sensitive to the GOF effects of GNAS-Gsa.

FC3.2

CFTR loss-of-function has effects on microRNAs (miRNAs) that regulate genes involved in growth, glucose metabolism and in fertility in *in vitro* models of cystic fibrosis

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Cystic Fibrosis (CF), is due to CF-transmembrane-conductance-regulator (CFTR) loss-of-function. Significant heterogeneity exists between patients, suggesting potential epigenetic regulation, and comorbidities develop with time. MiRNAs are non-coding RNAs that act as epigenetic regulators. Although many studies have focused on the role for miRNAs in regulating CFTR gene expression, little attention has been given to how CFTR influences their expression and how this affects growth, glucose metabolism and fertility.

We aimed to assess changes in miRNA expression levels dependent on CFTR loss-of-function, and to subsequently identify the affected molecular pathways.

CFBE41o-(homozygous for F508del mutation), and IB3(heterozygous for F508del/W1282X mutations) human immortalized cell lines were used since they reflect the most common genetic mutations in humans for CF, and 16HBE14o- (derived from normal bronchus) cells as controls. RNA was isolated from each cell line (miRVana kit). Global miRNA profiles were assessed using Taq-Man Array Human MicroRNA Card Set v3.0 which enable accurate quantitation of 754 human miRNAs. Relative quantification was performed using U6snRNA and RNU48 as endogenous controls and 16HBE14o- cells as calibrator for relative abundance of each miRNA which was calculated as fold change (\log_{2}^{DDCt}). MiRNAs showing fold-changes of $\geq +2$ or ≤ -2 ($p\text{-value}\leq 0.05$) were considered. MiRNA target genes and KEGG pathways were identified using miRWalk software and DIANA-mirPathv.3 web-server, respectively.

In CF cell lines, 41 miRNAs showed significant changes, 17 were up-regulated and 24 down-regulated. Ten miRNAs were regulated in both CFBE41o- and IB3 cells, and a subset of 3 showed significant differences between the two CF cell lines (miR-200b, miR-616, miR-942). Further, 14 miRNAs were regulated in CFBE41o- only and 17 in IB3 only, suggesting genotype-specific effects.

The 41 miRNAs targeted genes within pathways involved with longitudinal growth (TGF-beta, mTOR, MAPK, Prolactin, and PI3K-Akt signaling pathways), glucose metabolism (Hippo signaling, Fatty acid biosynthesis, FoxO signaling) and fertility (Oocyte meiosis, Estrogen signaling, Progesterone-mediated oocyte maturation). Interestingly, within the growth regulating pathways, genes involved with genetic short stature in humans were highlighted (BRAF, FLNB, GNAS, NF1, PDE3A, RAF1,

STAT5B, IGF1R) as well as genes involved with glucose metabolism dysregulation (FOXO1, FOXO3, G6PC, GSK3B, IRS1, IRS2, IRS4), and infertility (ESR1, PGR, Cyclins, BCL2, Caspases).

In conclusion, CFTR loss-of-function determines changes in the miRNA network and thus on gene regulation. Changes are related with the specific genetic mutations and have effects on genes involved with longitudinal growth, glucose metabolism and fertility which can show alterations in CF patients.

FC3.3

Variability in drug metabolizing cytochrome P450 activities caused by Human Genetic Variations in NADPH Cytochrome P450 Oxidoreductase (POR)

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Background: A broad spectrum of human diseases, including abnormalities in steroidogenesis, are caused by mutations in the NADPH cytochrome P450 oxidoreductase (POR) (1-2). Cytochrome P450 proteins perform several reactions, including metabolism of steroids, drugs and other xenobiotics. Therefore, genetic variations in POR can impact many different metabolic pathways by changing the activities of cytochromes P450 (1). In 2004 the first human patients with defects in POR were reported, and over 200 variations in POR are known (2).

Methods: By analyzing the POR sequences from sequencing projects, we identified potentially disease-causing variations and characterized these by functional studies using recombinant proteins. Proteins were expressed in bacteria and purified for activity assays. Activities of cytochrome P450 enzymes were tested in liposomes prepared with lipids into which P450 and P450 reductase proteins were embedded and assayed using fluorogenic substrates on a microplate spectrofluorometer.

Results: Here we are reporting the effect of POR variants on drug metabolizing enzymes CYP2C9, CYP2C19, and CYP3A5 which are responsible for the metabolism of many drugs. POR Variants A115V, T142A, A281T, P284T, P284L and A287P and Y607C inhibited activities of all P450 proteins tested. Interestingly, the POR variant Q153R showed a reduction of 20-50 activities with CYP2C9 and CYP2C19 but had a 400% increased activity with CYP3A5. Similarly, the common polymorphism in POR, A503V showed several fold higher activities with all drug metabolizing P450s studied.

Conclusions: The A287P is most common POR mutation found in patients of European origin, and significantly inhibited drug metabolism activities have important consequences for monitoring and treatment of patients. Similarly, higher drug metabolism activities from A503V variant of POR suggests monitoring the patients with this variant carefully. The A503V is the common polymorphism in POR present in about 25% of all alleles and is often ignored in diagnostic reports. These results indicate that detailed knowledge of POR effects is necessary for correct diagnosis and treatment options for persons with POR deficiency and the role of changes in drug metabolism needs to be addressed.

Changes in drug and steroid metabolism due to genetic variations can be addressed using personalized metabolic profiling and supplementation.

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FC3.4

Droplet digital PCR is a useful method for detection of mosaic mutations in patients with McCune-Albright syndrome

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Introduction: McCune-Albright syndrome (MAS) is caused by somatic mosaic mutations in the GNAS gene. Detection of the GNAS mutations is usually difficult because of the low frequency mosaicism. Droplet digital polymerase chain reaction (ddPCR) is a new technology that enables to measure absolute quantities of target nucleic acids in a sample by counting nucleic acid molecules encapsulated in discrete water-in-oil droplet partitions.

Objective: To investigate usefulness of ddPCR for detection of low-frequency mosaic GNAS mutations in patients with MAS.

Materials and Methods: We recruited a patient already diagnosed with MAS in this study. Sanger sequencing using DNA extracted from the thyroid gland revealed a somatic p.R201H mutation in GNAS in the patient. We performed ddPCR using DNA obtained from peripheral blood leukocytes. FAM- and HEX-labeled probes were designed for the mutant and wild-type alleles, respectively. Mixture of DNA and reaction reagents were generated into 20,000 droplets by using Droplet Generator, and amplified as manufacturer's protocol. After the amplification, each droplet was measured for fluorescence intensities one by one by Droplet Reader. The droplets including the mutant or wild-type allele indicate strong amplitude of FAM or HEX, respectively. The mutant allele frequency was calculated by comparing the number of FAM-positive droplets from the total number of either FAM- or HEX-positive droplets. Next, the detection sensitivity of ddPCR was examined by diluting patient's DNA with control DNA. In order to further improve the detection sensitivity, we performed a nested PCR method using PNA (peptide nucleic acid) prior to ddPCR.

Results: The ddPCR assay demonstrated that frequency of the p.R201H mutation was 9.4% in peripheral leukocytes DNA in the patient. The detection limit of ddPCR was calculated to 0.2% by the diluting method. The detection limit of ddPCR was decreased to 0.005% after performing the nested PCR assay.

Conclusion: The present study provided evidence that the ddPCR is a powerful tool saving cost and time for detection of low-frequency mosaic mutations.

FC3.5

Evaluation of Endocrine Late Effects in Survivors of Childhood Allogeneic Hematopoietic Stem Cell Transplantation in Australia – Database from 1985 To 2011

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Background: With improved survival of childhood allogeneic hematopoietic stem cell transplant (HSCT), there is increasing need for surveillance, including assessment of endocrine late effects in this cohort^{1,2}.

Aim: To evaluate endocrine late effects after chemotherapy and radiation in survivors of childhood allogeneic HSCT.

Methods: Multi-site evaluation via medical record review and cross-sectional questionnaires filled by patients or parents of survivors of childhood allogeneic HSCT at the Royal Children's Hospital (RCH) Melbourne between 1985 and 2011, for past and current information from RCH and adult hospitals of current attendance.

Results: 230 survivors were identified, 54.8% responded to questionnaires. Median age at transplant for malignancy was 7.7 years, with median follow up of 11.3 years. For non-malignant conditions, median age at transplant was 3.9 years and median follow up of 13.0 years. Findings were summarized in the table.

Conclusion: We confirmed endocrine late effects after childhood HSCT in a large cohort followed for up to 29 years, were frequent, seen predominantly as gonadal dysfunction, poor bone health, overweight with metabolic syndrome. Other endocrine deficiencies and thyroid malignancy were common in those who received radiation. These findings underline an urgent need for careful surveillance and very long term follow-up of HSCT survivors.

References

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Endocrine late effects	HSCT for malignancies		HSCT for non-malignant conditions	
	Irradiated [^]	Radiation-naive	Irradiated [#]	Radiation-naive
Gonadal failure/dysfunction	80.0% (64/80)	44.4% (28/63)	50.0% (3/6)	22.9% (11/48)
Siring/Having pregnancy	10.2% (6/59*)	20.6% (7/34*)	0% (0/5*)	9.8% (4/41*)
Short stature	35.6% (26/73)	31.0% (18/58)	33.3% (1/3)	29.1% (16/55)
Panhypopituitarism	7.6% (6/79)	0% (0/62)	0% (0/6)	0% (0/58)
Growth hormone/GHRH deficiency	27.5% (22/80)	1.6% (1/62)	16.7% (1/6)	10.3% (6/58)
2 ⁺ adrenal insufficiency	9.0% (7/78)	3.3% (2/61)	0% (0/6)	1.7% (1/58)
Thyroid USG abnormality	45.5% (35/77)	1.7% (1/60)	60% (3/5)	0% (0/58)
Thyroid malignancy	16.9% (13/77)	0% (0/60)	20% (1/5)	0% (0/57)
Thyroid dysfunction	44.0% (33/75)	12.5% (8/64)	16.7% (1/6)	5.2% (3/58)
Overweight	33.8% (23/68)	25.0% (14/56)	33.3% (1/3)	14.8% (12/81)
Hyperlipidemia	49.4% (38/77)	15.3% (9/59)	16.7% (1/6)	20.7% (12/58)
Diabetes Mellitus/Impaired fasting glucose	10.7% (8/75)	1.7% (1/59)	0% (0/6)	6.9% (4/58)
Osteoporosis/Osteopenia	16.9% (13/77)	19.0% (11/58)	0% (0/6)	14.5% (8/55)
Vitamin D deficiency/insufficiency	16.9% (13/77)	17.2% (10/58)	33.3% (2/6)	35.7% (20/56)

[^]16 of 87 survivors received cranial irradiation additional to total body irradiation (TBI)

[#]6 survivors received TBI only

*Only those ≥18 years included in denominator

FC3.6**Severe Infections Contribute to Increased Risk of Early Death in Patients with Apeced**

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Introduction: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a rare autosomal recessive disease that is characterized by a combination of various endocrinopathies and other autoimmune disease components. Few longitudinal studies have shown a decreased life expectancy in APECED. However, knowledge on mortality and causes of death in patients with APECED is scarce.

Objective: Our aim was to describe the mortality and causes of death among Finnish APECED patients and to describe the life-time incidence of severe infections.

Patients: The study included the cohort of patients originally described by Perheentupa and patients identified by contacting pediatric endocrine departments. Causes of death were collected from Statistics Finland. Patient records were reviewed for the clinical course of the disease and the incidence of infections requiring hospital treatment. To compare the incidence of infections in the surviving patients, we compared data with that of 44 patients with APECED who had participated our cohort study on bone health during 2015-2016.

Results: Altogether 97 Finnish patients with APECED were identified. In total, 33 of the patients had deceased during 1967-2018. Median age at death was 36 years (range 10.9 – 62.9). Causes of death were reported for 29 cases. The most common immediate cause of death was infection ($n=7$, 24%). Other common immediate causes of death included APECED (5), accidents (4) and cardiovascular events (4). Median age at death among those deceased with infection as the immediate cause of death was 23 years whereas for patients who had another cause of death the median age of death was 43 years ($p=0.088$). The most common infection as a cause of death was pneumonia (3 deaths). Other infections as causes of death included meningitis, septic infection, upper respiratory tract infection and myocarditis. When we compared the deceased patients with the surviving cohort of patients, the age [median 37.8 years (range 7.0-70.1)] and the number of disease components [median 6 components (2-10) vs. 6 (1-10)] did not differ between the groups. Altogether 73% of deceased patients had had severe infections in comparison to 68% of living patients. The median number of severe infections did not differ significantly between deceased and living patients [median 2 infections (0-13) vs. 1 (0-8), $p=0.136$].

Conclusion: Patients with APECED have a significantly increased risk of dying younger than average population. The most common immediate causes of death are infections, fatal accidents, cardiovascular events and APECED itself. Severe infections are common among all APECED patients.

Fat Metabolism and Obesity Session

FC4.1**Involvement of visfatin in adipose tissue fibrosis through modulation of extracellular matrix proteins**

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Introduction: Obesity development and subsequent white adipose tissue (WAT) expansion is often accompanied by WAT fibrosis which leads to adipocyte dysfunction. Fibrosis is a condition in which extracellular matrix (ECM) proteins are increased aberrantly and results in immune cell infiltration, cytokine production and insulin resistance. Visfatin is an adipokine that is implicated in obesity and its metabolic consequences; however, its role in WAT fibrosis has not been previously explored.

The aim of this study was to evaluate the levels of visfatin and its correlation with endotrophin as the secretory part of collagen IV in obese children and adolescents and to investigate the effect of visfatin on the gene and protein expression of the main proteins involved in fibrosis in adipocytes and pre-adipocytes.

Methods: 60 subjects (30 obese, 30 control) were enrolled after clinical and anthropometric evaluation and their plasma levels of visfatin and endotrophin, as well as lipid profile and insulin resistance parameters were measured. For the cellular studies, 3T3-L1 pre-adipocytes were cultured and treated with 200 ng/ml recombinant visfatin in serum-free medium. Cells were also differentiated to adipocytes using medium enriched with isobutylmethylxanthine, dexamethasone, and insulin. Cell viability was assessed by MTT. Gene expression levels of collagen IV, osteopontin, and matrix metalloproteinases (MMP) 2, 9 were analyzed by real-time PCR after RNA extraction and cDNA synthesis. Expression of ECM proteins was measured by western blotting.

Results: plasma levels of endotrophin and visfatin were higher in obese subjects compared with control subjects. A significant positive correlation was found between visfatin and endotrophin. Visfatin was also positively correlated with indices of insulin resistance including glucose, insulin, and HOMA-IR. Visfatin increased the gene and protein expression of collagen VI and osteopontin in pre-adipocytes. In order to evaluate the signaling mechanism of visfatin, cells were treated with the inhibitors of major signaling pathways, one hour prior to visfatin treatment. The results showed that visfatin exerts its effect on collagen VI gene expression through PI3K, JNK, and NF- κ B pathways, while induces osteopontin gene expression via PI3K, JNK, MAPK/ERK, and NOTCH1 signaling pathways. Visfatin also induced gene expression of MMP-2 and MMP-9 in pre-adipocytes.

Conclusion: Visfatin increases the expression of ECM proteins and therefore is involved in WAT fibrosis and remodeling. The relationship between visfatin, endotrophin and insulin resistance parameters in obesity as well as the cellular findings suggest that the WAT fibrosis might serve as a link between visfatin and insulin resistance.

FC4.2

Characterization of the adipose progenitor cell marker *MSCA1* in normal weight and obese children

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Background: Obesity is characterized by an increase in fat mass caused by an increase in adipocyte number and adipocyte size and is often associated with adipose tissue (AT) dysfunction contributing to metabolic impairment. It is suspected that adipocyte progenitor cells play an important role during healthy and obesity-related AT expansion. Studies in adults showed that the stroma vascular fraction (SVF) of AT is composed of different progenitor cell subpopulations with different abilities to proliferate and differentiate. We want to characterize the adipose progenitor cell marker *MSCA1* as an obesity-related factor in AT of lean and obese children.

Methods: The percentage of adipocyte progenitor cells within the SVF we determined by flow cytometry using the specific surface marker *MSCA1*. In addition, we investigated a possible association between *MSCA1* expression in isolated adipocytes and cells of the SVF and serum levels of *MSCA1*, measured by ELISA, in lean (n=35) and obese (n=30) children of our Leipzig Childhood AT cohort.

Results: Based on previous studies of Anne Bouloumié-Diehl et al., we established a protocol for isolating adipocyte progenitor cells in SVF from subcutaneous AT (scAT). We detected, similar to these studies, $12.6\% \pm 3\%$ (mean \pm SEM) *MSCA1* positive adipocyte progenitor cells in SVF from scAT of adult women (n=7). Moreover, we measured *MSCA1* expression in scAT samples as well as serum levels in lean and obese children. *MSCA1* expression increases with increasing age of the children in SVF cells ($p<0.05$) and adipocytes ($p<0.001$). We observed no gender-specific differences in the expression of *MSCA1*. Interestingly and in accordance with adult studies, adipocyte *MSCA1* expression was significantly higher in obese compared to lean children. For the expression of *MSCA1* in SVF cells, however, no significant correlation between lean and obese children was obtained. Our data showed no association between *MSCA1* expression in AT and circulating *MSCA1* in the serum. We could not find a significant difference in serum levels between obese and lean children.

Conclusions: In conclusion higher adipocyte *MSCA1* expression but not *MSCA1* serum levels and SVF *MSCA1* expression are related to obesity in children. Currently, we are investigating whether AT *MSCA1* expression and/or serum levels are suitable as a surrogate marker for the number of *MSCA1* positive progenitor cells in AT of children.

FC4.3

Circulating Growth-and-Differentiation Factor-15 in Early Life: Relation to Prenatal and Postnatal Size

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Background: Growth-and-differentiation factor-15 (GDF15) is a regulator of energy homeostasis, and is used as biomarker of several pathological states.

Objectives: To assess longitudinally GDF15 concentrations in a cohort of infants born either appropriate- (AGA, n=70) or small-for-gestational-age (SGA, n=33), the latter known to be at increased risk for central adiposity and metabolic alterations, particularly when they experience a rapid postnatal catch-up in weight.

Methods: Assessments included body length, weight, and ponderal index (PI); fasting glucose, insulin, IGF-I, HMW-adiponectin, GDF15; body composition (by absorptiometry) at birth, 4, 12 and 24 months.

Results: GDF15 levels at birth were significantly higher than those at each subsequent time point ($p<0.001$), and were similar in AGA and SGA subjects. GDF15 levels dropped at age 4 months, particularly in SGA infants ($p=0.008$ vs AGA), and continued to decline progressively in both subgroups reaching adult concentrations by age 24 months. GDF15 levels correlated inversely with the changes in PI and IGF-I at each time point, and with the gain in body fat over 24 months.

Conclusions: Early life is associated with supra-adult concentrations of GDF15. The reduced levels of GDF15 in SGA subjects early in postnatal life may be an adaptive mechanism to promote food intake and postnatal catch-up in weight, favoring a positive energy balance. Further follow-up will disclose whether this outcome may increase the risks for obesity later in life.

FC4.4**The rs72613567:TA variant in the hydroxysteroid 17-beta dehydrogenase 13 gene reduces liver damage in obese children**

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Background: The rs72613567:TA variant in the *hydroxysteroid 17-beta dehydrogenase 13* (*HSD17B13*) gene has been associated with decreased risk of liver damage.

Aims: To investigate the association between the *HSD17B13* rs72613567:TA variant and both hepatic steatosis and biochemical markers of liver damage in obese children and to evaluate its potential effect in NAFLD genetic predisposition.

Methods: 684 obese children were genotyped for *HSD17B13*, *patatin-like phospholipase domain containing 3* (*PNPLA3*) gene, *transmembrane 6 superfamily member 2* (*TM6SF2*), and *membrane bound O-acyltransferase domain containing 7* (*MBOAT7*) polymorphisms and underwent anthropometrical, ultrasonographic, and biochemical evaluation. Indirect measurement of liver fibrosis (Pediatric NAFLD Fibrosis Index [PNFI]) was calculated. The population was clustered in two risk groups (group 1 including subjects carrying up to 3 risk alleles and group 2 including subjects carrying 4-6 risk alleles).

Results: Carriers of the *HSD17B13* rare A allele showed lower serum ALT and AST levels than noncarriers, even after adjustments for confounding factors (A carriers ALT mean \pm SD 26.58 \pm 18.02, noncarriers 31.83 \pm 20.64; p=0.001; A carriers AST mean \pm SD 23.32 \pm 8.13, noncarriers 25.75 \pm 9.66; p=0.001). Likewise, these patients showed a lower percentage of hepatic steatosis (carriers 27.1%, noncarriers 72.9%, p=0.0001) and a significant lower PNFI levels than noncarriers (A carriers mean \pm SD 7.57 \pm 2.94, noncarriers 7.99 \pm 2.35, p=0.04), even after adjustments for confounding factors (p=0.03).

Similar findings were confirmed in the study population stratified on the basis of the genetic risk score. In fact, both in the group 1 and 2, the patients carrying the *HSD17B13* rare A allele presented a statistically significant lower serum ALT levels, PNFI levels, and a lower percentage of liver steatosis compared to noncarriers with the same genetic risk score.

Conclusion: We demonstrated in childhood obesity the protective effect of the rs72613567:TA variant in *HSD17B13* gene in reducing liver damage in obese children even regardless of genetic predisposition.

FC4.5**Leptin Gene Methylation Status In Egyptian Infants**

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Background: Obesity results from interactions between environmental and genetic factors. Despite a relatively high heritability of common, non-syndromic obesity (40–70%), the search for genetic variants contributing to susceptibility has been a challenging task. To date, more than 40 genetic variants have been associated with obesity and fat distribution. However, since these variants do not fully explain the heritability of obesity, other forms of variation, such as epigenetics marks, must be considered. DNA methylation is one of the best-understood epigenetic mechanisms and an important programming mechanism of the genome, in which cells and tissues can adapt to past and present environmental exposures. The methylation of the leptin gene promoter suppresses its expression and decrease in leptin production is highly associated with obesity.

Aim: The study aimed to study the leptin gene methylation status in a six-month-old cohort of Egyptian infants.

Patients and Methods: The study was carried on 50 infants aged 6-month-old, attending the outpatient clinic of Alexandria University Children's Hospital. All infants joined the study were subjected to full history taking, thorough clinical examination stressing on anthropometric measurement. Peripheral blood samples were taken for genetic analysis to study the methylation status of leptin gene promoter by methylation-specific polymerase chain reaction (MS-PCR) at 31 nt at 51 nt loci

Results: Out of 50 infants 25 were exclusively breastfed and 25 were artificially fed. A significantly higher percentage of formula-fed infants were methylated in leptin gene promoter at 31 nt locus compared with breastfed infants. Also, at 51nt locus infants with methylated leptin gene had significantly higher weight for length standard deviation score compared to infants with methylated gene

Conclusion: Leptin gene is unmethylated in breastfed infants compared to formula-fed infants. So epigenetics mechanisms could play a role in the development of obesity.

FC4.6**Brain Satiety Responses to a Meal in Children Before and After Weight Management Intervention**

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Family-based behavioral treatment (FBT) is the recommended intervention for children with obesity (OB). However, there is a large variability in short- and long-term treatment response and

mechanisms for unsuccessful treatment outcomes are not understood. We studied brain regions involved in satiety processing in 9–11-year-old children with obesity (OB, n=54) and children with healthy weight (HW, n=22). Subjects underwent a functional magnetic resonance imaging scan to examine response to visual food cues followed by a test meal and then a second scan. In OB children, neuroimaging procedures were repeated after ending 6-months of FBT. Mean extracted neural activation for the contrasts of high- and low-calorie food cues vs. objects were assessed across *a priori* brain regions of interest: ventral and dorsal striatum, amygdala, ventral tegmental area/substantia nigra, insula and medial orbitofrontal cortex. Forty OB subjects completed FBT. At the end of FBT, 55% of OB children showed clinically significant reductions in BMI z-score of -0.125 or more. However, even after successful treatment, over two-thirds of children increased their BMI z-score 6–12 months after ending FBT. FBT responders reduced their leptin (mean) from 32.9 to 18.9 ng/ml ($p<0.0001$), potentially contributing to subsequent weight regain, while in non-responders leptin increased from 33.8 to 37.6 ng/ml. At baseline pre-FBT, OB vs. HW children exhibited an attenuated average central response to a satiating meal in which they did not reduce activation by high-calorie food cues across the *a priori* regions ($p<0.01$). Among OB subjects greater pre-treatment extent of pre- to post-meal reduction of neural activation by high-calorie food cues (i.e., similar to the response of HW children) predicted better BMI z-score reduction at the end of FBT ($p=0.03$). However, a stronger BMI z-score reduction in FBT was associated with a worsened brain satiety response after treatment ($p=0.03$), potentially predisposing, even children who were initially responsive to FBT, to increased subsequent motivation to eat and weight regain. These findings implicate an attenuated central satiety response in OB vs. HW children and that the brain's response to a meal can predict FBT treatment outcomes in OB children. An impaired central satiety response can be a barrier to immediate and sustained FBT treatment success. Clinicaltrials.gov #NCT02484976. Supported by R01DK098466 (CLR); R01DK089036 (EAS), and P30DK035816 (University of Washington Nutrition and Obesity Research Center).

large 'blocking' dose that prevents endogenous thyroid hormone synthesis, requiring thyroid hormone replacement (block and replace or BR), or in a smaller dose that renders the patient euthyroid (dose titration or DT). The American Thyroid Association (ATA) recommends DT because of the reduced risk of side effects on the lower TA dose. Whether BR provides advantages in terms of improved biochemical stability in the young, growing patient is unknown.

Method: We conducted a multi-centre phase III, open-label randomised trial comparing BR with DT in newly diagnosed patients with thyrotoxicosis less than 17 years (y) old who were recruited at 15 United Kingdom units. 81 patients (12 aged 2 to 9y and 69 aged 10 to 16y) were randomised to BR or DT shortly after diagnosis and then treated with ATD for 3 years. The primary outcome for each patient was the proportion of TSH levels in the local reference range for visits (scheduled every 3 months) between 6 months and 3 years. Secondary outcomes included the proportion of FT4 levels in the reference range, frequency of adverse events and outcome (remission/relapse) at 4y.

Results: 81 patients (62 Female) were randomised, 40 to BR (20 with a FT4 ≥ 50 pmol/l) and 41 to DT (19 with a FT4 ≥ 50 pmol/l); 7 were lost to follow-up, 3 withdrew from the trial with 1 ineligible. The mean proportion of serum TSH within reference range was 60.2% (BR patients) compared to 63.8% (DT patients); adjusted difference 4.3%, $p=0.48$, 95% CI (-7.8,16.4). Corresponding quantities for FT4 were 79.2% (BR patients) compared to 85.7% (DT patients); adjusted difference 6.8%, $p=0.13$, (-0.2,15.6). 45 patients (23 BR, 22 DT) reported at least one adverse event related or possibly related to ATD: for these patients the median number of such AEs was 3 (BR) & 2 (DT). 3 patients developed neutropenia in the BR group (none in DT). 6 BR and 10 DT patients were in remission at 4y. 17 BR and 24 DT patients relapsed. 13 remained on ATD beyond 3 years (9BR, 3DT).

Conclusions: This trial has shown no evidence to suggest that BR is associated with improved biochemical stability. DT, as recommended by the ATA, is the preferred approach to TA administration in growing people with thyrotoxicosis in the longer term.

Thyroid

FC5.1

Randomised Trial of Block and Replace versus Dose Titration antithyroid drug treatment in children and adolescents with thyrotoxicosis

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Background: First line treatment for thyrotoxicosis is thionamide (TA) antithyroid drug therapy. The TA used is usually Carbimazole in the UK. TA can be administered in a relatively

FC5.2

Lower proportion of CD19+IL-10+ and CD19+CD24hiCD27+ IL-10+, but not CD1d+CD5+CD19+CD24+CD27+ IL-10+ B cells in children with autoimmune thyroid diseases

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Introduction: Hashimoto's thyroiditis (HT) and Graves' disease (GD) become increasingly common in children's population. Pathogenesis of autoimmune thyroid diseases (AITD) bases on coexistence of genetic predisposition and environmental triggers

which finally drive to breakdown of immune tolerance. Many mechanisms in human body moderate process of inflammation. While some of them answer for up-regulation, some agents like B regulatory lymphocytes (Bregs) inhibit spreading of inflammation. Bregs represent 5-10% of whole population of B lymphocytes ($CD19^+$) and one of their particular feature is production of interleukin 10 (IL-10) thus they can control inflammation and autoimmunity. The importance of Bregs in the population of children with AITD remain unexplored. The aim of this study was to estimate the expression of Bregs (phenotype $CD19^+CD24^{hi}CD27^+IL-10^+, CD19^+IL-10^+, CD1d^+CD5^+CD19^+IL-10^+$ and $CD1d^+CD5^+CD19^+CD24^+CD27^+$) in pediatric cohort with AITD and health controls.

Methods: A total of 100 serum samples were obtained from 53 pediatric patients with GD (N=12 newly diagnosed, mean age 12.5 ± 3.5 and N=17 during methimazole therapy, mean age 12.7 ± 4.4), HT (N=10 newly diagnosed, mean age 13.3 ± 2.9 and N=10 during L-thyroxine therapy, mean age 13.7 ± 3.4) and compared with healthy controls (C) (N=15, mean age 13.1 ± 3.1). The expression of the immune cells populations were analyzed by the four-color flow cytometry using a FASC Canto II cytometer (BD Biosciences). Statistical analysis of the acquired data was performed with the use of GraphPad Prism 5.01 software (GraphPad Software Inc., San Diego, CA).

Results: There is decreasing tendency in number of B10 cells among all B lymphocytes (phenotype $CD19^+$) and more widely, also among all lymphocytes, in every studied group, comparing to C. We report notable reduction of IL-10 production in Bregs cells with expression $CD19^+IL-10^+, CD19^+CD24^{hi}CD27^+IL-10$ and $CD1d^+CD5^+CD19^+IL-10^+$ in both untreated and treated AITD. In case of $CD1d^+CD5^+CD19^+CD24^+CD27^+$ impairment in IL-10 production in treated GD and HT groups was noted.

Conclusion: Our data demonstrate that both number and functionality of Bregs in children's AITD are disturbed. The reduction in number of Bregs with $CD19^+CD24^{hi}CD27^+IL-10^+$ and $CD19^+IL-10^+$ expression could be responsible for dysregulation of the immune system and contribute to AITD development.

Article has been submitted to the Thyroid.

FC5.3

Predominant DICER1 Mutations in Pediatric Follicular Thyroid Carcinomas

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Background: Pediatric thyroid cancer has characteristics that are distinct from adulthood thyroid cancer. Due to its very low prevalence, little is known about the genetic characteristics of pediatric follicular thyroid cancer (FTC).

Methods: We investigated genetic alterations in tumor tissues from 15 patients aged < 20 years (median: 14.3 years; range: 2.4–19.0 years) using multifaceted approaches. Whole-exome sequencing, targeted next-generation sequencing using a cancer gene panel, and Sanger sequencing of the major exons of the *H/K/N-RAS* and *DICER1* genes and the promoter region of the *TERT* gene, were performed. Normal tissues and blood of patients with *DICER1*-positive tumors were also evaluated to determine the germline *DICER1* mutation.

Results: The median tumor size was 3.1 cm (range: 0.6–6.4 cm). Four patients exhibited angioinvasion, and one extensive capsular invasion; none showed evidence of disease over a median of 7.6 years. Eight patients (53.3%) had *DICER1* mutations, including four with *DICER1* syndrome (three patients were <10 years of age). A *PTEN* frameshift mutation (n = 1), *PAX8/PPAR γ* rearrangement (n = 1), and multiple loss of heterozygosity with or without copy number alterations (n = 2) were detected. No *RAS* or *TERT* mutations were found. Nodular hyperplasia and follicular adenoma (FA) coexisted in *DICER1* mutation-positive FTCs more frequently than mutation-negative FTCs (p=0.026). All *DICER1* mutation-positive FTCs had a somatic missense mutation at metal binding sites (six at codon E1813 and two at codon D1709) within the RNase IIIb domain; seven had other missense, nonsense, or frameshift mutations in the *DICER1* gene. Six coexisting FAs of two patients with *DICER1* syndrome (three of each) had additional somatic mutations at metal binding sites within the RNase IIIb domain (codon E1705, D1709, D1810 or E1813), different from each other and from the indexed FTC tumor.

Conclusions: Pediatric FTCs had distinct genomic alterations and pathogenesis compared to adults, particularly those characterized by *DICER1* mutations. The *DICER1* mutation should be considered in pediatric FTCs, especially in cases < 10 years of age. In all *DICER1*-mutated FTCs and FAs, recurrent hotspot mutations were found at metal binding sites within the RNase IIIb domain, suggesting their impact on tumorigenesis.

FC5.4**Thyroid dysgenesis : Exome-wide analysis identifies rare variants in genes involved in thyroid development and cancer**

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Context: Congenital hypothyroidism from thyroid dysgenesis (CHTD) is mainly a sporadic and non-syndromic condition occurring in 1:4,000 live births. In contrast to rare cases of syndromic monogenic CHTD, non-syndromic (NS) CHTD shows low familial recurrence risk (~2%) and low concordance rate between MZ twins, suggesting a two-hit scenario combining post-zygotic events with either a *de novo* monogenic mutation or incomplete penetrance of polygenic inherited variants. This latter possibility was recently proven right in cases of non-syndromic congenital heart defects.

Objective: To evaluate whether a burden of rare disruptive variants is observed in cases of NS-CHTD.

Methods: We compared the exome of 36 cases of NS-CHTD (33 with ectopy and 3 with athyreosis) to that of 495 controls of French-Canadian ancestry to assess the enrichment of rare variants in NS-CHTD by gene burden analysis. Next, we selected disruptive variants by multiple haploinsufficiency tests. Then, genes expressed in thyroid tissue were prioritized.

Results: Gene-based burden testing showed an enrichment of rare variants in 31 genes in the NS-CHTD cases. On the other hand, multiple haploinsufficiency tests found enrichment of disruptive variants in 15 genes. Based on expression in thyroid tissue, 3 of these 15 genes are either overexpressed in thyroid cancers (*ATF5* and *FOXK1*) or involved in cell migration (*PLXNA4*).

Conclusions: Our data suggest that: (i) a burden of disruptive variants contributes to the risk of NS-CHTD and (ii) *ATF5* and *FOXK1* have a divergent function in thyroid development and cancer.

FC5.5**Identification of *TRPC4AP* as a novel candidate gene causing thyroid dysgenesis**

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Background: Congenital hypothyroidism (CH) is the most common endocrine disorder in neonates and is predominantly caused by developmental abnormalities known as thyroid dysgenesis (TD). Several transcription factors have been described in its aetiology, but defects in the known genes only account for a small proportion of cases.

Methods: To identify novel genes involved in TD, we performed exome sequencing in 7 unrelated patients with CH due to TD and their respective parents. After filtering the raw data, the functional effects of the most relevant variants were predicted using the *in silico* prediction tools MutationTaster, SIFT, PolyPhen2, PROVEAN, and CADD. The most promising candidate gene, *TRPC4AP*, was sequenced in a cohort of 200 unrelated Caucasian patients with TD, diagnosed in the German newborn screening program. Expression of *TRPC4AP* in thyroid tissue was performed using RT-PCR. *Trpc4ap*- functional analysis was performed in *Xenopus laevis* using morpholinoantisense oligomers.

Results: *TRPC4AP* was considered as a promising candidate gene. Targeted sequencing of *TRPC4AP* in a cohort of 200 patients with TD demonstrated gene variants with predicted damaging potential: one mutation leading to a *de novo* stop codon p.Q552*.

and four additional mutations resulting in an amino acid exchange (p.P706S, p.F729L, p.S777C, and p.N229S). Three of them were transmitted from a phenotypically unaffected parent. We could also demonstrate that *TRPC4AP* is expressed in human thyroid gland tissue. Using *Xenopus laevis* as an animal model, we could show that the volume of the tadpole thyroid gland was reduced by 20% in *Trpc4ap* morpholino knockdowns compared to controls. One of the 7 patients carried two known variants with predicted functional relevance in the *PAX8* gene (p.I34T, V35I); both were transmitted by the affected mother.

Discussion: *TRPC4AP* encodes a 797-amino acid protein, which is expressed in various tissues including thyroid. A putative interaction of *TRPC4AP* and the NF-kappa-B- essential-modulator (NEMO) encoded by the *IKBKG* gene was identified by IPA analysis. *IKBKG* plays a role in the activation of the NF- κ B-signaling pathway and regulates various genes involved in thyroid development.

Conclusion: *TRPC4AP* was identified as a novel candidate gene in TD, but further functional studies are needed for validation

FC5.6

Homozygous loss-of-function mutation in the SLC26A7 gene coding a novel iodide transporter causes goitrous congenital hypothyroidism

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Introduction: Iodide transport in the thyroid is crucial for thyroid hormone synthesis. A homozygous loss-of-function mutation in the *SLC26A4* gene coding an iodide transporter located at the apical side in the thyroid follicular cells causes Pendred syndrome accompanied with goitrous congenital hypothyroidism (CH) and sensorineural deafness. However, about half of patients with Pendred syndrome demonstrate normal thyroid function. This indicates another iodide transporter at the apical side in the thyroid

follicular cells. We identified a homozygous nonsense mutation in the *SLC26A7* gene in siblings with goitrous CH. We also showed that *SLC26A7* functioned as an iodide transporter at the apical side in thyroid follicular cells together with *SLC26A4*.

Patients: Patient 1, a 15-day-old male neonate, born to unrelated nonconsanguineous parents, was suspected of CH following neonatal mass screening. The initial laboratory results showed extremely high serum thyroid-stimulating hormone levels (TSH, >100 μ IU/mL) and low free thyroxine levels (FT4, 0.64 ng/dL) with goiter identified by ultrasonography. Patient 2, the younger sister of the proband, was a 5-year-old girl. She visited our institution because of an obvious goiter. Her neonatal mass screening was normal. The initial laboratory examination showed elevated serum TSH (31.79 μ IU/mL), significantly low serum FT4 (0.18 ng/dL), and extremely elevated serum thyroglobulin levels (2600 ng/mL). Both patients currently take LT4 supplementation.

Methods and Results: We conducted whole exome sequencing on the siblings with goitrous CH, their healthy sibling, and their parents. We identified a homozygous nonsense mutation of the *SLC26A7* gene (c.1498C>T; p.Gln500Ter) in the affected siblings. The unaffected mother, father, and sibling carried the mutation in a heterozygous state. Because *SLC26A7* was expressed mostly in the thyroid according to the NCBI database and belongs to the same SLC26 family as *SLC26A4*, we speculated that *SLC26A7* acted as an iodide transporter. We identified *SLC26A7* expression at the apical side in thyroid follicular cells using immunohistochemical staining in normal human thyroid tissue. Using iodide transport assays, electrophysiological and optical experiments, we demonstrated that *SLC26A7* transported iodide according to the concentration gradient. In HEK293T cells, the mutant (p.Gln500Ter) localized in the cytosol while the wild type localized in the membrane. We also confirmed the defective iodide transporter activity of the mutant by transiently expressing an iodide-sensitive YFP mutant (YFP-HQ/IL).

Conclusion: We conclude that *SLC26A7* is a novel iodide transporter and its dysfunction causes goitrous congenital hypothyroidism.

Bone, Growth Plate and Mineral Metabolism Session 2

FC6.1

Bone tissue characterization of a mouse model of atypical type VI osteogenesis imperfecta reveals hypermineralization of the bone matrix, elevated osteocyte lacunardensity and altered vascularity

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Objectives: Osteogenesis imperfecta (OI) is an extremely heterogeneous connective tissue disorder characterized by low bone mass, which together with altered bone matrix properties leads to skeletal fragility. Due to the wide range of symptoms, the pathophysiology of the OI is not fully understood. Null mutations in *SERPINF1*, encoding the potent antiangiogenic factor PEDF, cause type VI OI with excessive osteoid formation, abnormal osteoblast-osteocyte development and increased matrix mineralization. A very severe OI case has been reported recently with reduced PEDF secretion by osteoblasts, similar to OI type VI, but with normal PEDF serum levels. This atypical type VI OI was caused by a loss-of-function (p.S40L) in *IFITM5* the causative gene for type V OI. Six cases have been reported since then but it is unclear how the mutation impacts bone phenotype. To achieve further insights into the bone material properties, vascularization and thus pathophysiology of atypical type VI OI, we investigated a new knock-in (KI) mouse model carrying a leucine substitution for the BRIL p.Serine42 residue.

Methods: We analyzed longitudinal sections of distal femurs of 8 weeks-old heterozygous male mutants (KI, n=10) and wild-types (WT, n=9) using quantitative backscattered electron imaging (qBEI) performed with a scanning electron microscope (DSM962, Zeiss). Bone mineralization density distribution (BMDD) was measured in cancellous metaphyseal bone and midshaft cortical bone. The qBEI images were used to evaluate the osteocyte lacunae sections (OLS) in cortical bone and the structural histomorphometric parameters in cancellous bone. We used X-ray microcomputed tomography(micro-CT) to evaluate vascularization in the femoral third trochanter.

Results: qBEI revealed that bone matrix mineralization was significantly increased in KI compared to WT cancellous (CaPeak: +2.38%, P=0.0331) and cortical bone (CaPeak: +2.81%, P=0.0085; CaMean: +2.48%, P=0.0023; CaWidth: +11.24%, P<0.0001, CaHigh: +51%, P= 0.0027). We further observed in KI mice an in-

creased OLS density (+23.11%, P<0.0001) and decreased OLS mean area and perimeter (-20.25%, P<0.0001; -13%, P<0.0001, respectively) versus WT. Histomorphometry revealed no changes of mineralized BV/TV, BS/TV, Tb.N and Tb.Th between the two genotypes. Micro-CT analyzes yielded increased pore volume/bone volume in KI (+14.28%, P=0.044) mirroring increased vascularity.

Conclusion: Our new mouse model for atypical type VI OI has elevated bone matrix mineralization as in other forms of OI. The increased bone vascular volume is consistent with defective PEDF secretion in bone as reported in affected patients. Further analysis of osteoblasts function and osteoid formation will provide additional insights in atypical OI type VI.

FC6.2

Zone wise cell separation methods comparison, based on relative expression of specific growth plate markers in a pig model

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Introduction: Longitudinal skeletal growth is achieved by endochondral ossification in epiphyseal growth plates (GP) of long bones and vertebrae. These highly organized cartilaginous tissues contain chondrocytes of all differentiation stages classified in three distinct zones named resting, proliferative and hypertrophic. Separated analysis of individual zones is essential in basic GP research thus efficiency of different zonal separation methods confers high impact on study results. Nevertheless, lack of comparative studies on commonly used separation methods complicates the interpretation and comparison of basic GP research data.

Aim: We aim to compare the efficiency of two commonly used GP separation methods, density gradient centrifugation (DGC) and laser capture microdissection (LCM), by quantitative real time PCR (qRT-PCR) of zone-specific growth plate marker genes.

Methods: Primary chondrocytes and cartilage tissues were isolated from femoral and tibial growth plates of prepubertal piglets and separated by DGC and LCM, respectively. Relative gene expressions in samples were evaluated by qRT-PCR for Secreted Frizzled Related Protein 5 (Sfrp5) and Collagen type X (ColX) as markers for resting and hypertrophic zones.

Results: Both separation methods, DGC and LCM, were capable of generating resting and hypertrophic zone samples with significantly different marker gene expression compared to the adjacent zones, with the exception of Sfrp5 expression in proliferative versus hypertrophic zone measurements by both methods and Col X expression measurements in resting versus proliferative

zones by LCM. Both LCM and DGC could discriminate resting vs. proliferative zones by Sfrp5 expression values (DGC: $p=0.034$; LCM=0.003). Comparable results were observed for ColX gene expression levels in hypertrophic versus proliferative zones (DGC $p=0.024$; LCM<0.001). Two-way interaction testing between LCM and DGC revealed that, regardless of marker genes specific zonal expression difference is significantly different between two methods ($p = 0.001$). Similarly, marker genes expression showed a significant difference ($p = 0.004$) between both methods irrespective of growth plate zones investigated.

Conclusion: Taking all the above into account indicates that, while both methods are able to discriminate growth plate zones, LCM achieved substantially higher level of efficiency in zonal separation as compared to DGC. Thus, LCM is able to reduce methodological bias in and could be considered as preferred method for expressional studies on specific growth plate zones.

FC6.3

Decreased trabecular bone mineral density and muscle area at the forearm despite improvement in glycaemic control over 3 years after simultaneous pancreas kidney transplantation

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Background: Simultaneous pancreas kidney transplantation (SPKT) is a standard treatment option for young adults with type I diabetes (T1D) and concurrent renal failure. Despite the long-term immunosuppressive therapy the patients have better glycemic control, normalized renal function and an improved quality of life. Whether this is also reflected in the skeleton is not that clear yet.

Methods: Patients were prospectively followed after SPKT performed at a single tertiary center between November 2011 and December 2014. Besides routine blood tests, the subjects were scanned by DXA at the spine and by pQCT at the forearm within 2 months and then 1.3 and 3.3 years after the transplantation. One sample t-test was used to analyze the difference of the Z-scores of the bone parameters from zero and the difference between study start and end was tested by two-sample t.test.

Results: There were 32 patients (9 females) with T1D manifested at 18.3 ± 9.7 (mean \pm SD) years and aged 44.2 ± 9.6 years at the time of transplantation. The lumbar spine (LS) bone mineral density (BMD) was decreased at the baseline (Z-score -1.2 ± 1.3 , $p<0.001$), with 8/32 (25%) patients having BMD Z-score ≤ -2.0 ,

but normalized at study end (Z-score -0.2 ± 1.2 , $p=0.39$), with only 2/32 patients with Z-score ≤ -2.0 ($p=0.003$ vs. baseline). In contrast to LS BMD, trabecular volumetric BMD (vBMD) at the radius remained low over the study follow up (Z-scores -1.3 ± 1.2 at baseline and -1.3 ± 1.0 at study end, respectively, $p<0.001$ for both), with 9/32 (28%) and 8/32 (25%) participants, respectively, having the Z-score ≤ -2.0 . Similarly, the muscle area at the forearm was significantly decreased at both time points (Z-scores -2.2 ± 1.6 and -1.6 ± 1.4 , respectively, $p<0.001$ for both), with no improvement over the study period ($p=0.074$). Interestingly, glycated hemoglobin significantly improved after transplantation (67.8 ± 13.8 at study start vs. 38.9 ± 7.0 mmol/mol at study end, $p<0.001$).

Conclusions: This is the first study examining the development of volumetric, size independent, BMD in patients with T1D after SPKT. Despite the improvement in glycaemic control, the trabecular vBMD and muscle area at the forearm remained decreased even 3 years after SPKT, while LS aBMD increased. Areal BMD may falsely indicate fracture risk reduction. However, the relation of our findings of the BMD development to fracture risk in these patients remains to be elucidated.

FC6.4

Metabolically Unhealthy Obese Children and Adolescents Have Higher Bone Mineral Density Than Normal weighted controls but Lower than Metabolically Healthy Obesos: No Effect of FGF21 Levels

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Introduction: The harmful or beneficial effect of obesity on bone mineral density (BMD) is remain controversial in children and adolescence. Either increase or decrease of BMD have been reported. Several factors such as insulin resistance, prediabetes, high proportion of fat mass, sedentary lifestyle were suggested to cause the differences of BMD in obesity. FGF-21 is a metabolic factor that plays a specific role in the regulation of carbohydrate and lipid metabolism. However, the role of FGF-21 in bone metabolism seems somewhat paradoxical and complex. While improving of metabolic health, risk of reducing the bone health is suspected in experimental studies.

Objective: This study aims to find the differences of BMD from obese children and adolescent with metabolically healthy (MHO) and unhealthy obesities (MUO) compared to the healthy controls; and its relationship between metabolic parameters including serum FGF21 levels.

Methods: There were 92 participants for the obesity group and 44 for the control group; a total of 142 patients, aged 8 to 18 years. BMD, in addition to the routine obesity workup, which includes fasting blood glucose, fasting insulin levels, lipid profile and liver enzymes; serum FGF21 levels have been analysed. Being metabolically healthy was investigated either based on without “metabolic syndrome (MS)” and “Cardiometabolic risk factor clustering (CMRFC)”, and the correlation between BMD have been studied.

Results: Compared to the control group BMD z-score is significantly elevated in the obese group (1.19 ± 1.4 g/cm² vs 0.48 ± 1.7 g/cm², p:0.013). MHO had higher BMD z-score (obese without MS 1.22 ± 1.54 g/cm², obese without CMRFC 1.45 ± 1.7 g/cm²) than either MUO (obese with MS 1.09 ± 1.2 g/cm², obese with CMRFC 1.01 ± 1.2 g/cm²) and healthy controls (p:0.044, and 0.016). The FGF-21 were not significantly different among the participants who are MHO, MUO, and the control group (p>0.05). There are no significant difference between the FGF21 levels and bone density z-score levels among the male and female participants of obese and the control groups (p>0.05). The serum levels of fasting blood glucose, fasting insulin level, and lipids were not correlated to BMD z score.

Conclusion: Although we could not find any correlation among BMD-z score and metabolic parameters including insulin and FGF21 levels; being metabolically healthy was lead to have highest BMD. Even though the bone density levels are significantly elevated among the obese group compared to the control group, it is found that the bone density levels decline with deteriorating metabolic health parameters.

FC6.5

No change in bone density during 6 months off GH in adolescents with severe GHD at near-adult height

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Objective: Re-testing of childhood-onset GHD needs discontinuation of GH treatment at near-adult height. We recently reported significant changes of body composition as a consequence of severe GHD during this time period.

Aim: Does a 6 month interruption of GH treatment decrease bone quality significantly in patients with severe GHD of adolescence?

Patients and Methods: In 90 patients with childhood onset GHD treatment was stopped when patients reached near-adult height (HV <2cm/yr). After three months patients were retested with arginine-GHRH-test. After six months GH treatment was restarted in patients with a GH maximum <16 ng/ml and low IGF-1 (n=17, 4 females, mean age 16.3 yr). At stop of GH treatment and at 6 months off GH we performed a pQCT scan (XCT 2000 Stratec corp. Germany) of the non-dominant forearm at the 4 and 65% measure points. Measures of patients with severe GHD of adolescence were compared to that of patients with transient GHD of childhood (n=73, 15 females, mean age 17.1 yr.).

Results: In severe GHD of adolescence the trabecular density decreased from 214 to 202mg/cm³ (p<0.01); in transient GHD a similar decrease from 220 to 214 was observed (p<0.05). The trabecular density remained within the reference range in both groups.

In both groups increases were observed with respect to cortical density from 1077 to 1099 mg/cm³ (p<0.01) versus 1060 to 1079 mg/cm³ (p<0.001), with respect to strength strain index from 306 to 310 mm³ (n.s.) vs. 302 to 312 mm³ (p<0.05), and with respect to total bone area from 145 to 146 mm² (n.s.) vs. 153 to 155 mm² (n.s.). The changes of bone density and geometry were comparable.

Conclusion: Only trabecular density decreased significantly during 6 months off GH in all patients, independent of their GH status. Therefore we conclude that discontinuation of GH treatment for confirmation of the diagnosis does not harm the bone.

FC6.6**Craniosynostosis in inactivating PTH/PTHrP Signaling Disorder 2: a non-classical feature to consider**

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Classic features of inactivating PTH/PTHrP Signaling Disorder 2 or 3 (iPPSD2, iPPSD3), i.e. former pseudohypoparathyroidism include multi-hormone resistance, short stature, subcutaneous osifications, brachydactyly, and early-onset obesity and a molecular defect at the GNAS region. In addition, patients may present with less-known features including craniosynostosis (CSO).

Objective: To describe the prevalence of CSO in a cohort of 90 iPPSD2 and iPPSD3 patients, followed in one reference center. To describe the characteristics of the CSO in 8 iPPSD2 patients, recruited from 3 reference centers with data about the iPPSD2 disease.

Results: Six out of 71 iPPSD2 (8.4%) and none of the 19 iPPSD3 patients, had CSO. 7/8 and 1/8 patients with CSO carried a maternal and a paternal GNAS mutation, respectively. The 7 patients with CSO (**Table 1**) and a maternal GNAS mutation, presented with a severe iPPSD2 phenotype associated to the typical PTH resistance. We characterized cognitive impairment in 8/8, sleep disturbances in 6/8, and congenital hypothyroidism in 4/8. CSO was discovered before the diagnosis of iPPSD2 in 4/8.

Comments: In this large cohort of iPPSD2 and 3 patients, we found a significant prevalence of CSO. CSO seems associated with disease severity. As it was detected only in patients with loss-of-function in the GNAS gene, it is likely that the impaired PTH/PTHrP in skull bone is involved. Our findings have clinical relevance. We suggest that regular head circumference-for-age, and, if necessary, fundus oculi, should be performed in children with iPPSD2. Furthermore, CSO could be the first manifestation of iPPSD2, raising the need for calcium homeostasis evaluation in children with CSO of unknown origin. Early diagnostic and follow-up of these complex patients may improve their clinical care.

Table 1. Characteristics of the 8 patients (4 females) with craniosynostosis (CSO) and iPPSD2

	GNAS mutation	Origin	Age at diagnostic iPPSD2 (years)	Hormonal resistances	Chiari 1 anomaly	CSO	Synostosis sutures	Age at diagnostic CSO (years)
1	Exon 1	Novo	0.5	PTH, TSH	yes	complex	Sagittal-coronal	4.9
2	Intron 5	Novo	3	PTH, TSH, Gonadotrophins	no	complex	Sagittal	antenatal
3	Exon 7	-	7	PTH, TSH	-	complex	pansynostosis	<2
4	Intron 3	mat	0.1	PTH, TSH	no	complex	Sagittal-lambdoid	1
5	Exon 11	mat	0.5	PTH, TSH, Gonadotrophins	yes	complex	pansynostosis	1.5
6	Exon 5	mat	0	PTH, TSH	no	simple	Coronal	6.5
7	Exon 1	-	1.5	no	no	simple	Coronal	<1
8	Exon 7	Novo	2	PTH, TSH, ACTH	yes	complex	Sagittal-coronal	<2

Diabetes and Insulin Session 2

FC7.1

Deployment of a predictive model based on CpG methylation haplotypes analysis on the insulin gene promoter, in a cohort of children and adolescents with type 1 diabetes

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Background: Cytosine-guanine(CpGs) sites in molecules identified as methylated or unmethylated; the combination of them in the genetic sequence of an individual includes a methylation haplotype (methyl-haplotype) for a specific locus. The insulin gene promoter(IGP) is highly regulated by methylation mechanisms, which lead to alteration of gene expression.

Aim: To identify IGPmethyl-haplotypes among children/adolescents with type 1 diabetes(T1D) and to deploy a predictive model for the classification of cases and controls, using Next-Generation Sequencing(NGS)- methyl-haplotypes as biomarkers.

Patients-Methods: DNA from peripheral whole blood of 40 participants (20 T1D/20 healthy age-gender-matched) was extracted and IGP-region was sequenced by NGS; the sequence readings analysis was performed using FASTQ files. A python-based pipeline for targeted deep bisulfite sequenced amplicons(ampliMethProfiler) was applied to estimate the methylation status. Methylation profile at 10 CpG sites proximal to transcription start site of the IGP was recorded (*site 1/-357, site-2/-345, site 3/-234, site 4/-206, site 5/-180, site 6/-135, site 7/-102, site 8/-69, site 9/-19, site 10/+60*). Methylation of each site was coded as 0(zero) for unmethylation or 1(one) for methylation. A single read with the 10 CpG sites could result in “1111111111”methyl-haplotype(all methylated), in “0000000000”methyl-haplotype(all unmethylated) or any other combination. The generated methyl-haplotypes were tested as predictive biomarkers in five different classifiers (Random forest, Support Vector Machine Radial and Linear, Generalized Linear Regression, Linear Discriminant Analysis). Predictive models were evaluated with the Receiver Operating Characteristics for 10-fold cross validation; their performance was assessed by computing the metrics accuracy, sensitivity and specificity as a mean of 100 repetitions of random separation of the dataset in train and test set.

Results: 469 different methyl-haplotypes were recorded. After normalization of the features according to the number of readings, three distinct methyl-haplotypes: “1110101110”, “1110111110”and “1111111100”were more closely related to T1D compared to the controls (Wilcoxon test p-values: 0.00018,0.00032, 0.00095,

respectively); they were then used as predictors for the training of the five classifiers. The Support Vector Machine Radial presented the best accuracy (0.82 ± 0.09) and a balanced performance between the two categories having sensitivity 0.86 ± 0.12 and specificity 0.77 ± 0.15 .

Conclusions: Since methylation quantification approaches are unable to reflect the complexity of the methylation substrate, methyl-haplotypes describe in a more holistic manner the epigenetic profile of an individual. Methylation based biomarkers, such as IGP methyl-haplotypes 1110101110, 1110111110 and 1111111100 could serve as a strategy to identify individuals at high risk for β-cell failure.

FC7.2

Copeptin kinetics and its relationship to osmolality during rehydration for diabetic ketoacidosis in children: an observational study

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Background: Copeptin is a surrogate marker for arginine vasopressin (AVP) release in response to hyperosmolal stimuli such as diabetic ketoacidosis (DKA). We aimed to characterize the temporal course (kinetics) of serum osmolality and copeptin during rehydration and insulin therapy in children with type 1 diabetes (T1D) and DKA, and the relationship between both (dynamics).

Methods: An observational multi-center study was conducted including pediatric patients with T1D admitted for DKA and aged 1-18 years. Serial serum copeptin and osmolality measurements were taken at 14 time points from the start of rehydration therapy to 72 hours post rehydration start. Clinical parameters such as age, severity of DKA (mild = pH<7.3, moderate = pH<7.2, or severe pH<7.1) and Glasgow Coma Scale (GCS) were documented. Copeptin and osmolality kinetics and dynamics were further characterized using linear and non-linear mixed-effect regression modelling.

Results: Twenty-eight children with T1D (20 newly diagnosed) and DKA (mild: n=3, moderate: n=12, severe: n=13) were included in the study. Median [IQ range] age was 11.5 years [8, 14], GCS was 15 points [15, 15], no patient had GCS <12 or suffered from cerebral edema. 275 paired serum copeptin and osmolality measurements were obtained (median: 10 per patient). Kinetics were described by a mono-exponential decline (95%CI) [inter-indi-

vidual variability, expressed as coefficient of variation]: Copeptin decreased from 98 pmol/L (58.4-137.6) [142%] to 10.3 pmol/L (8.8-11.8) [25%] with a 50% recovery time ($t_{1/2}$) of 6.0 h (5.1-11.5) [98%]. Serum osmolality decreased from 321 mosmol/L (315-327) [4%] to 294 mosmol/L (292-296) [1%] with $t_{1/2}$ of 4.3 h (3.0-5.6) [64 %]. Bi-exponential decrease was also tested, but did not show clear improvement compared to mono-exponential decline given available data (large standard errors in parameter estimates). Dynamics were described as exponential increase: copeptin levels doubled with each osmolality increase by 15 mosmol/L (10-27) [50%], baseline copeptin levels were 9.2 pmol/L (8.0-10.4) [2%] at 280 mosmol/L.

Conclusions: This is the first data set available on sequential copeptin levels in a hyperosmolar state in children. Copeptin and osmolality decreased in parallel during rehydration and insulin therapy in pediatric patients with DKA. Physiologic maximum copeptin response was not observed despite wide osmolality range, suggesting a large synthesis and release capacity of AVP in children. These data underline the usefulness of copeptin as a surrogate marker of hyperosmolar triggered AVP release and as a potential marker to guide rehydration therapy.

FC7.3

MicroRNA circulating levels in children at diagnosis of type 1 diabetes

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Background: Type 1 diabetes (T1D) is a chronic disease characterized by autoimmune destruction of pancreatic beta-cells. Dysregulated miRNA levels have been described in T1D patients, though results are inconclusive.

Objective and Hypotheses: The aim of this study was to assess the circulating profile of different miRNAs in children at diagnosis of T1D.

Method: 27 children with T1D onset (16M/11F) and 26 controls (16M/10F) underwent anthropometric, biochemical and metabolic evaluation. Insulin antibodies (IAA), glutamic acid decarboxylase antibodies (GAD), and islet tyrosine phosphatase-2 antibodies (IA2) were assessed in T1D patients. Serum levels of several miRNAs (miR-21, miR-181, miR-25, miR-126, miR-148, miR-486, miR-345, miR-222, miR-140, miR-454, miR-125, miR-636, miR-500, miR-375 and miR-383) were analyzed by qPCR.

Results: Age was not different between T1D and control subjects (6.9 ± 3.9 yrs vs 6 yrs ± 2.8 yrs, $p=0.313$) as well as weight (-0.43 ± 1.06 SDS vs -0.16 ± 1.46 SDS, $p=0.458$) and height (0.22 ± 1.39 SDS vs 0.76 ± 3.8 SDS, $p=0.513$). MiRNA serum levels were similar between females and males except for miR-500, significantly higher in males than females ($p=0.03$). MiR-126 was lower in T1D patients ($p=0.016$) whereas miR-486 and miR140 were higher in T1D subjects compared to controls ($p<0.05$). In T1D male subjects miR-21 serum levels were lower compared to controls

($p=0.003$). In T1D subjects, miR-21 correlated with IA2 ($r=0.468$, $p=0.032$) and GAD antibodies ($r=0.423$, $p=0.05$). miR-140 correlated with C-peptide levels ($r=0.991$, $p=0.009$), HDL-cholesterol levels ($r=0.958$, $p=0.042$) and Triglycerides/HDL ratio ($r=0.993$, $p=0.007$).

Conclusions: T1D subjects have a different circulating miRNA profile compared to age, gender and weight matched controls. miR-140 is upregulated at T1D onset and correlates with residual beta cell function. The observed relationships of miRNAs with islet cell autoantibodies and metabolic parameters warrant further investigations to evaluate their possible use either as predictors or as markers of disease progression.

FC7.4

Metabolic syndrome features in pre-pubertal children born after maternal pre-eclampsia

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Background: Pre-eclampsia is associated with important complications for both mother and baby in the short term, but there are limited data about its long-term effects on offspring metabolism. Thus, we aimed to assess whether maternal pre-eclampsia was associated with adverse effects on metabolism and body composition in the offspring in childhood.

Methods: We studied healthy pre-pubertal children (aged 4–10 years) born at term. Offspring of mothers who were diagnosed with pre-eclampsia ($n=39$) and offspring of mothers from control pregnancies ($n=50$) were compared. Primary outcome was insulin sensitivity measured using intravenous glucose tolerance tests and Bergman's minimal model. Other assessments included body composition using whole-body dual-energy x-ray absorptiometry, 24-hour ambulatory blood pressure monitoring and lipid profiles.

Results: Children born after maternal pre-eclampsia had lower insulin sensitivity compared to controls [9.86 vs $12.56 \times 10^{-4} \cdot \text{min}^{-1} \cdot (\text{mU/l})$; $p=0.046$], as well as higher fasting insulin concentrations [5.64 vs 3.24 mIU/l ; $p<0.001$] and HOMA-IR [1.18 vs 0.70 ; $p=0.004$]. In addition, children born after pre-eclamptic pregnancies had higher diastolic blood pressure in the daytime (+4.6 mmHg; $p=0.013$) and night-time (+8.6 mmHg; $p<0.0001$), higher mean arterial pressure in the night-time (+7.0 mmHg; $p<0.001$), and lower nocturnal diastolic dipping (10.6 vs 16.2%; $p=0.040$), as well as higher triglyceride levels (0.75 vs 0.62 mmol/l; $p=0.016$). However, children in the two groups had similar anthropometry and body composition.

Conclusion: Our study shows for the first time that maternal pre-eclampsia is associated with lower insulin sensitivity and elevated fasting insulin levels in the pre-pubertal offspring. In addition, we observed abnormalities in 24-hour ambulatory blood

pressure monitoring. As the aetiology of pre-eclampsia becomes clearer, relating these to childhood outcomes will be critical. Further studies are required to follow-up the offspring born after pre-eclampsia to ascertain whether the observed differences track into adolescence and adulthood.

FC7.5

Is the 1-hour post-load glucose level by 75g oral glucose tolerance test a new risk factor in predicting atherosclerosis?

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Background and Objectives: Recent studies demonstrated that a 1-hour post-load plasma glucose (1-h PG) value of ≥ 155 mg/dL during an oral glucose tolerance test (OGTT) is a new risk factor for predicting atherosclerosis. Herein, we evaluated whether individuals with normal glucose tolerance (NGT), whose 1-h PG is ≥ 155 mg/dL, or with impaired glucose tolerance (IGT) have an increased carotid intima-media thickness (CIMT), as compared with NGT individuals with 1-h PG < 155 mg/dL.

Material and Methods: Obese adolescents at risk for prediabetes were administered a 75g OGTT. CIMT was measured in all patients on the same day with OGTT. Individuals with prediabetes were identified according to fasting plasma glucose concentration and/or HbA1C (5.7-6.4%). Patients with diabetes were excluded from the study. Subsequently, subjects were divided in 3 groups: that have NGT with a 1-h PG < 155 mg/dL, have NGT with a 1-h PG ≥ 155 mg/dL, and have IGT.

Results: The study included 171 obese adolescents with prediabetes (74 males, 97 females; mean age: 13.5 ± 1.8 years). Seventy-three patients were NGT with a 1-h PG < 155 mg/dL, 29 patients were NGT with a 1-h PG ≥ 155 mg/dL and 69 patients were IGT. No statistically significant difference was found between the groups in terms of age, weight, height and BMI ($p > 0.05$). As compared with NGT individuals with a 1-h PG < 155 mg/dL, NGT individuals with a 1-h PG ≥ 155 mg/dL exhibited higher CIMT (0.75 ± 0.15 mm vs. 0.68 ± 0.15 mm; $P = 0.025$). No significant differences were observed in CIMT between IGT and NGT subjects with a 1-h PG ≥ 155 mg/dL (0.75 ± 0.18 mm vs. 0.75 ± 0.15 mm; $p > 0.05$). Of the three glycemic parameters, 1-h and 2-h PG, but not fasting glucose, were significantly correlated with CIMT.

Conclusion: These data suggest that a cutoff point of 155 mg/dL for the 1-h PG during OGTT may be a useful tool to identify a subset of individuals at higher risk of developing cardiovascular disease.

Key words: Prediabetes, obesity, 1-hour post-load plasma glucose, intima-media thickness

FC7.6

2017 American Academy of Pediatrics Clinical Practice Guideline: Impact on Prevalence of Arterial Hypertension in Children and Adolescents with Type 1 Diabetes mellitus

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Background: In 2017 the American Academy of Pediatrics has introduced a new guideline (AAP 2017) to diagnose arterial hypertension in children, as the blood pressure thresholds for adults had been lowered before. There is a controversy about these new reference levels as other societies have not followed these recommendations. We studied the impact of the new AAP 2017 guideline on prevalence of arterial hypertension (HTN) in children with Type 1 diabetes mellitus (T1DM).

Methods: Up to September 2018, 1.4 million office BP measurements of 79849 children and adolescents (aged 5-20 years) with T1DM have been documented in the DPV registry. BP values of the most recent year were aggregated, BP of 74677 patients without antihypertensive medication were analyzed (median age 16 yrs., diabetes duration 5.3 yrs., 52.8% boys). BP values were classified according to AAP 2017, the references of the German KIGGS (2011) and the 4th report (2004).

Results: 44.1%, 29.5% and 26.5% of the patients were hypertensive according to AAP 2017, KIGGS and 4th report, resp. Differences in prevalence of HTN were strongly age depended: <10 years: AAP 2017 31.4%, KIGGS 30.7%, 4th report 19.6%, 10-<15 years: AAP 2017 30.9%, KIGGS 31.2%, 4th report 22.4% and ≥ 15 years AAP 2017 53.2%, KIGGS 28.4%, 4th report 30.0%. Among teenagers ≥ 15 years, 59.1% of the boys but only 46.3% of the girls were classified as hypertensive by AAP 2017 but based on KIGGS/4th report only 21.1%/26% of the boys and 36.7%/34.4% of the girls, resp.

Conclusion: Classification of BP as hypertensive depends strongly on the references. AAP 2017 results in a significant increase HTN in teenagers ≥ 13 years with T1DM, particularly in boys. AAP 2017 enhances the awareness for elevated BP in children, particularly in patients with increased risk for cardiovascular disease. Elevated BP should prompt further evaluation, but not the immediate start of antihypertensive medication.

Pituitary, Neuroendocrinology and Puberty Session 1

FC8.1

Hypothalamic AgRP Neurons Drive Endurance in Food-restricted Mice

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Diseases of food restriction, such as anorexia and bulimia nervosa, are psychiatric conditions with the highest mortality. It is not known how these disorders emerge and what determine mortality. Individuals with these disorders frequently engage in compulsive exercise. States of food restriction are associated with elevated activity of hypothalamic neurons that produce AgRP, which cells are crucial for feeding and can promote stereotypic behaviors.

Here, we interrogated whether these hypothalamic neurons are involved in sustained compulsive exercise during food restriction. Using a combined pharmacologic and genetic approach, we found that regardless of AgRP circuit activity, food-restricted animals engaged in compulsive exercise if a running wheel was available, but there was a positive correlation between AgRP circuit activity and exercise volume. Strikingly, animals with impaired AgRP circuitry died of exhaustion after few days of compulsive running, while those animals, in which we activated AgRP neurons daily, had significantly increased endurance of compulsive exercise compared to all other groups without lethality during the trial.

As a mechanistic cause of the involvement of AgRP neurons in endurance exercise, we found that these cells are crucial for proper mobilization of lipids from fat stores, a known determinant of endurance running.

These observations shed new light on a previously unsuspected organizational role of AgRP neurons in the regulation and dysregulation of complex behaviors via both neuronal and systemic actions with direct implications for psychiatric conditions such as anorexia nervosa.

FC8.2

Analysis of Hypothalamic Metabolic Circuits after Normalization of Body Weight in Mice that had been Obese due to high fat diet intake

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The obesity epidemic continues to be a dramatic problem in the developed world despite attempts to curtail its rise. Reducing energy intake and/or increasing energy expenditure can result in weight loss; however, if one returns to their poor lifestyle habits the previous weight is not only recuperated, but often surpassed.

We hypothesized that although a normal body weight may be achieved, the hypothalamic circuits controlling appetite and energy expenditure may not return to normal, at least in the same time-frame.

To this end, male and female 7-week old C57/BL6J mice were fed a high fat diet (HFD; 60% kcal from fat, 20% kcal from carbohydrates, 5.1 kcal/g) or standard rodent chow (3.1 % kcal from fat, 76% kcal from carbohydrates, 3.41 kcal/g) for 2 months. Then, half of the HFD group was returned to the normal chow diet (HFDCH). All mice were killed one month later, with a glucose tolerance test (GTT) being performed one week before. Hypothalami were processed for real time PCR. At two months all HFD mice had gained significantly more weight than the chow mice. After the return to chow, HFDCH mice lost weight and after one month their weight was not different from chow mice. Although HFD increased fasting glucose in both sexes, only male HFD mice had an increased area under the curve in the GTT ($p<0.001$). Fasting glycemia and energy intake of HFDCH mice normalized one month after the diet changed. Females had higher hypothalamic mRNA levels of neuropeptide Y (NPY) and Agouti-related peptide (AgRP) than males (both $p<0.0002$), with HFD decreasing the expression of these neuropeptides in both sexes. The change from HFD to chow increased AgRP expression to control levels in both sexes. In females NPY mRNA returned to control levels, but in males NPY expression was only partially normalized. Proopiomelanocortin (POMC) mRNA levels were higher in males than females and decreased on the HFD only in males ($p<0.004$) and remained reduced one month after being changed to chow. In females there were no differences in POMC mRNA levels between dietary groups.

In conclusion, there is a clear sex difference in the response of hypothalamic metabolic neuropeptides to dietary changes. Although a normal weight is obtained, the hypothalamic metabolic control system, especially in males, remains altered. Thus, this could result in a more dramatic increase in weight gain if returned to a less healthy lifestyle.

FC8.3**Absence of central adrenal insufficiency in adults with Prader-Willi syndrome**

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Introduction: Individuals with Prader-Willi syndrome (PWS) suffer from hyperphagia, hypotonia and hypothalamic dysfunction, leading to a variety of pituitary hormone deficiencies. Central adrenal insufficiency (CAI) has been reported in PWS, while each of these studies used different testing modalities and cut-off values. Therefore, reported prevalence of CAI ranges from 0% to 60%. It has been speculated that CAI might be responsible, at least in part, for the high mortality (3%) in patients with PWS. If CAI is present, timely diagnosis and treatment is needed in order to prevent avoidable mortality. There are no guidelines on the appropriate evaluation and management of CAI in adults with PWS. In our center, many adult patients with PWS receive standard hydrocortisone (HC) treatment around physical and/or psychological periods of stress. Frequent administration of HC increases the risk of obesity, hypertension, osteoporosis and diabetes, already a major problem in adults with PWS. It is therefore of utmost importance to assess the real prevalence of CAI in order to prevent both under- and overtreatment with HC.

Methods: We performed multiple dose metyrapone (MTP) test in 42 patients and insulin tolerance test (ITT) in 9 patients. When levels of 11-DOC during MTP were greater than 230 nmol/L (7.6 g/dL) or levels of cortisol during ITT were greater than 500 nmol/L (18.1 µg/dL), adrenal insufficiency was excluded.

Results: 51 adult subjects (31 males and 20 females), median (range) age 29.2 (18.9 – 58.3) yrs, with genetically confirmed PWS, participated in the study. 22 subjects (43%) were using GH treatment since childhood. Using the MTP or ITT, CAI was excluded in all subjects. Even patients with a low baseline cortisol level (lowest: 119.0 nmol/L) appeared to have a normal MTP/ITT test result. MTP test/ITT were tolerated well by all individuals. Additional revision of medical files of all PWS adults visiting our tertiary referral center (n = 120) revealed that none of the patients who underwent surgery without peri-operative hydrocortisone treatment had suffered complications due to hypocortisolism.

Conclusion: Central adrenal insufficiency appeared to be absent in all 51 adults with Prader-Willi syndrome tested by multiple dose metyrapone test or an insulin tolerance test. This indicates that CAI is rare in adults with PWS. Based on these results, we recommend performing a MTP or ITT test before prescribing hydrocortisone medication during periods of psychological or physical stress in all adults with PWS.

FC8.4**Peripheral and Hypothalamic Alterations in The Insulin-Like Growth Factor (Igf) System in Response to High Fat Diet-Induced Weight Gain**

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The insulin-like growth factor (IGF) system is fundamental for physiological processes such as growth and metabolism. In addition, in the brain it regulates glucose metabolism and neuroprotection. The IGF axis can be altered by nutritional status, but little is known regarding the effects of specific dietary components on this system.

Our aim was to examine how high-fat diet (HFD) and low-fat/high sucrose diet (LFHSD) intake affect the central and circulating IGF systems.

Male and female 7-week old C57/BL6J mice were fed a HFD (60% kcal from fat, 20% kcal from carbohydrates, 8.9% of weight from sucrose, 5.1 kcal/g), LFHSD (10% kcal from fat, 72% kcal from carbohydrates, 33.1% of weight from sucrose, 3.76 kcal/g) or standard rodent chow (3.1 % kcal from fat, 76% kcal from carbohydrates, 0.9% of weight from sucrose, 3.41 kcal/g) for 2 months. A glucose tolerance test (GTT) was performed a week before sacrifice. Plasma hormone levels were assayed by ELISA and relative gene expression by RT-PCR.

HFD increased weight gain and visceral and subcutaneous adipose tissue levels in both sexes ($p<0.001$) compared to chow and LFHSD. Energy intake was higher on the HFD in both sexes, reaching significance in females ($p<0.001$). Glucose tolerance was impaired only in males on the HFD ($p<0.01$). Plasma levels of free ($p<0.001$) and total ($p<0.001$) IGF1 were higher in HFD mice of both sexes, with HFD also increasing insulin ($p<0.05$) and IGFBP3 ($p<0.01$) levels. HOMA-IR was impaired by HFD in both sexes ($p<0.05$).

In the hypothalamus, IGF1 mRNA levels were increased after HFD consumption ($p<0.05$) in both sexes and by LFHSD only in females ($p<0.05$). Also in females, IGF2 ($p<0.05$) and IGFBP2 ($p<0.01$) mRNA were increased by HFD consumption compared to both chow and LFHSD. In all mice, relative IGF2 and IGFBP2 were positively correlated ($r=0.843$, $p<0.001$). In males, IGFBP5 mRNA levels increased in LFHSD and HFD compared to chow ($p<0.01$). No changes in other members of the IGF family were observed.

In conclusion, the central and peripheral IGF systems are modulated in HFD-induced weight gain, with this effect differing between males and females. In females, the HFD-induced increase in

IGF2 and IGFBP2 expression in the hypothalamus, a glucose sensing region, deserves further investigation as these factors have been implicated in glucose metabolism and could possibly be involved in the increased ability of females to maintain a normal GTT even with a significantly increased body weight.

FC8.5

LGR4-Wnt β -catenin signalling directs GnRH network development, with defects leading to self-limited delayed puberty

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Background: The initiation of puberty is dependent upon an augmentation of gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus. Development of the GnRH neuroendocrine network in embryonic life depends on coordinated migration of neurons from the vomeronasal organ in the nose to the forebrain. We have previously demonstrated that dysregulation in GnRH neuronal migration leads to delayed pubertal onset. Late puberty affects up to 2% of the population and results in adverse health outcomes. Self-limited delayed puberty (DP) (i.e. constitutional delay of puberty) runs in families, most commonly with autosomal dominant inheritance patterns, indicating a strong genetic basis of the trait. However, the genes underlying DP remain mainly unknown.

Aims and Methods: To discover novel genetic mutations in pathways regulating GnRH neuronal migration and development in our large, accurately phenotyped cohort of patients with DP. Whole exome sequencing was performed on DNA from 160 individuals of 67 multi-generational families affected with DP. Variants returned were analysed to identify rare, potentially pathogenic variants enriched in case versus controls and with biological relevance to GnRH neuronal development pathways. The candidate gene *LGR4*, identified via this strategy, was investigated via *in silico* and *in vitro* techniques and via a mouse model.

Results: We identified three rare missense variants in *LGR4* in four unrelated families (14 affected individuals) and all segregated with DP trait with the expected autosomal dominant pattern of inheritance. These variants are highly conserved and were predicted to be deleterious by the main prediction software tools

(SIFT and POLYPHEN 2). *In vitro* analysis of *Lgr4* revealed specific expression in mice olfactory epithelium and vomeronasal organ at different embryonic stages. The LGR4 mutants showed an impaired Wnt β -catenin signalling, due to defective protein expression, a shorter protein half-life (p.I96V and p.G363C mutants) and defective trafficking to the plasma membrane (p.G363C and p.D844G mutants). Moreover, we investigated the role of *Lgr4* in a knock-out mouse model: *Lgr4*^{+/-} mice had a delayed onset of puberty and fewer GnRH neurons compared to *Lgr4*^{+/+} mice, both in early embryogenesis and at the hypothalamus, whereas *Lgr4*^{-/-} mice failed to enter puberty and showed a significant reduction in GnRH neurons.

Conclusions: Defects in *LGR4*, acting via the Wnt signalling pathway, affect GnRH neuron development in foetal life, resulting in a phenotype of self-limited DP. Our findings contribute to the ongoing exploration of genetic factors controlling pubertal timing.

FC8.6

Source and Changes in Serum Level of Kisspeptin in Female Rats at Different Developmental Stages

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Introduction: The *Kiss1*/Kisspeptin/*Kiss1r* system is essential for puberty onset and reproductive system development, especially in the hypothalamus. Nevertheless, *Kiss1* is expressed in other organs. Additionally, serum kisspeptin has been associated with puberty. However, studies on the developmental changes in serum kisspeptin levels and its main source are limited. Therefore, the aim of this study was to evaluate the developmental changes of serum kisspeptin and identify its main source.

Methods: ELISA was used to analyze serum kisspeptin levels at the onset, and mid-way of each different stage (days 4, 8, 14, 23, and 27, and during vaginal opening). Tissues (known to express *Kiss1*) from several organs were recovered at the same time points. The expression of *Kiss1* mRNA in these tissues were compared with the pattern of serum kisspeptin levels. In addition, ovariectomy (OVX) was performed on day 14, half of the ovariectomized rats were treated with estradiol (E2), and changes in serum kisspeptin levels in OVX or OVX + E2 rats evaluated. To identify the main source of serum kisspeptin, the changes in hypothalamic *Kiss1* expression were evaluated and compared to that of serum kisspeptin.

Results: Serum kisspeptin levels increased with increasing developmental stages till the pre-pubertal stage. Several organs expressed *Kiss1* mRNA, with the expression pattern in ovaries being similar to that of serum kisspeptin levels. After OVX, serum kisspeptin levels decreased with or without E2 treatment. These changes were different from anteroventral periventricular nucleus (AVPV) and arcuate nucleus (ARC) *Kiss1* mRNA expression changes.

Conclusions: Ovarian *Kiss1* may be main source of serum kisspeptin, which may double as a downstream marker of ovarian reproductive function development.

Fetal, Neonatal Endocrinology and Metabolism (to Include Hypoglycaemia)

FC9.1

Using CRISPR/Cas9 gene editing to study the molecular mechanisms of Congenital Hyperinsulinism (CHI)

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Background: Congenital Hyperinsulinism(CHI) is characterised by the unregulated secretion of insulin in the presence of hypoglycaemia. The mutations in ABCC8 and KCNJ11, which encode the sulfonylurea receptor 1 (SUR1) and potassium inward-rectifying 6.2 (Kir6.2) subunits of ATP-sensitive potassium channel (K channel), are the most common identified cause of the condition. Defects in the HADH gene are responsible for SCHAD- HI, a rare form of the disease caused by the disruption of fatty acid oxidation.

Aims: The aim of this project is to use the novel CRISPR/Cas9 gene editing technique to create a KO mouse cell model of Congenital Hyperinsulinism. The two genes of interest are ABCC8 and HADH. This cell model would be used for molecular and functional interrogation and may further aid in development of novel therapeutic drugs for CHI.

Methods: Three CRISPR sgRNAs were designed to target both genes of interest. Optimisation of the delivery of CRISPR/Cas9 system included the evaluation of different formats such as plasmid DNA, mRNA and RNP complex using a reporter gene. At the molecular level, the disruption of the gene was confirmed by T7 Endo assay. Single cell cloning is being attempted prior to Sanger sequencing. As a pilot, optimisation of ELISA using wild type (WT) β TC6 cells to demonstrate glucose-stimulated insulin secretion (GSIS) has been undertaken. Optimisation of Western Blot analysis looking for reduced protein expression is being undertaken concurrently.

Results: Progress so far has addressed the optimisation of transfection conditions to deliver CRISPR/Cas9. LPR nanocomplexes were used successfully for the first time in the transfection of β TC6 cells.

The molecular validation of Abcc8 and Hadh KO models has been demonstrated by heteroduplexes in the T7 Endo assay. In addition, the optimisation of the ELISA insulin assay in wild type β TC6 cells has demonstrated a dose dependent GSIS which can be used as a standard to compare the GSIS from the KO cell model.

Conclusions: The results of our study so far has demonstrated the potential of the use of Cas9/gRNA system as an efficient reverse genetic tool in studying the molecular mechanisms underlying CHI. Our future aims are to: conduct further molecular interrogation to confirm the KO in Abcc8 and Hadh gene; and further, use the newly generated KO mutant cells to analyse the function of these genes and furthermore, to test and develop novel therapeutic drugs for CHI.

FC9.2

Heterozygous Insulin Receptor (INSR) Mutation associated with Neonatal Hyperinsulinaemic Hypoglycaemia and Familial Diabetes Mellitus

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Introduction: Mutations in Insulin Receptor (INSR) is usually associated with insulin resistance and hyperglycemia. Homozygous or compound heterozygous mutations in INSR are usually linked with Rabson-Mendenhall or Donohue syndromes whilst heterozygous INSR mutations are associated with type A insulin resistance. Various autosomal dominant heterozygous INSR mutations leading to hyperinsulinaemic hypoglycemia (HH) have been described in adults and children but not in the neonatal period. The youngest age reported with HH and heterozygous INSR mutation is 3 years.

Case Presentation: A small for gestational age (SGA) child born to a mother with gestational diabetes presented with persistent neonatal hypoglycemia and was diagnosed with HH. The child's maternal grandfather had been diagnosed with type 2 diabetes mellitus at the age of 45 years and was treated with metformin. A good response to diazoxide was noted in the infant and on subsequent follow up, diazoxide was gradually weaned and discontinued by 8 months of age. The couple's second child presented with SGA and HH at birth responsive to diazoxide which remitted at 10 months of age. Both infants tolerated a 16 hour fast without hypoglycemia and with normal concentrations of plasma insulin and demonstrated no clinical evidence of insulin resistance at 2 and 4 years of age. The mother had normal body mass index (BMI 24 kg/m²). Maternal grandfather of the infants had a BMI of 25 kg/m². Neither adult showed clinical signs of insulin resistance. On genetic analysis, a heterozygous pathogenic INSR missense variant p.(Met1180Lys) was found in both infants, mother and grandfather, but not in the father.

Conclusion: We report, for the first time, an association between INSR mutation and transient neonatal HH. INSR mutations should be considered in patients with neonatal HH and a family history of diabetes mellitus. Follow up of these children is important to determine the natural history of progression and early diagnosis of diabetes or insulin resistance.

FC9.3**DNA methylation signatures in placenta and umbilical cord: association with maternal obesity**

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Background and Objectives: Offspring born to obese mothers are at an increased risk of chronic disease including type 2 diabetes (T2D), obesity, hypertension, cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD). This metabolic programming is produced, in part, by epigenetic changes such as DNA methylation. We postulated that obesity exposure impacts the offspring's methylome and used an epigenomic approach to explore this hypothesis in placenta and umbilical cord.

Methods: Placenta and umbilical cord samples were obtained from 24 mother-newborn pairs [8 with pregestational obesity and increased gestational weight gain (OB-OB), 8 with pregestational normal weight and increased gestational weight gain (Norm-OB) and 8 with pregestational normal weight and normal gestational weight gain (Norm-Norm)]. Women were recruited at the first trimester of pregnancy and followed until delivery. DNA methylation was measured at >850 000 CpG sites (Infinium® MethylationEPIC BeadChip). The association between the methylation status and maternal obesity was studied using beta regression models (with pregestational BMI as predictor and the methylation level of each CpG as response). DAVID bioinformatic analysis was conducted to study the possible functional roles of the differentially methylated genes (identification of significant metabolic pathways and potentially affected diseases/disorders).

Results: In all the study subjects pooled together in a group, pregestational BMI associated with the differential methylation of 1,031 CpG sites (742 genes) and 369 CpG sites (314 genes) in placenta and umbilical cord, respectively [false discover rate (FDR)-corrected P-value<0.05]. The differentially methylated genes in the placenta were involved in pathways related to cell growth and proliferation (MAPK, cGMP and cAMP) and had potential effect on metabolic disorders such as T2D, coronary heart disease and glycosylated hemoglobin (all p<0.05). The differentially methylated genes in the umbilical cord were involved in pathways related to cell proliferation and lipid metabolism (AMPk, FoxO, lipolysis, mTOR) and had a potential effect on metabolic diseases such as T2D, obesity and hypertension (all p<0.05).

Conclusions: Our results show that pregestational obesity may cause epigenetic alterations (DNA methylation) in placenta and umbilical cord genes involved in fetal growth and development, which may have potential effects on metabolic disorders. Perinatal epigenetic analyses may thus have utility in identifying individual vulnerability to later metabolic diseases.

FC9.4**Prenatal environment and genetic background influence urinary steroid excretion in monozygotic twins with intra-twin birth-weight differences**

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Background: Low birth-weight and unfavourable intrauterine conditions are associated with a subsequent impact on the endocrine system. Many studies reported hyperandrogenaemia and precocious adrenarche in children born small for gestational age (SGA). However, little information is available on steroid profiles in these subjects.

Objective and Hypotheses: We followed genetically identical twins with intra-twin birth-weight differences from birth until adolescence to objectify the impact of a lower birth-weight on development and health in later life.

Method: 68 monozygotic twin pairs were included in this study. Birth-weight difference of <1SDS was defined concordant (n=41, 18 female), birth-weight difference ≥1SDS discordant (n=27, 15 female). Spontaneous urine samples were collected at a mean age of 14.9 yrs and gas chromatography-mass spectrometry (GC-MS) was used to analyse urinary steroid profiles (36 metabolites).

Results: We found pronounced intra-twin correlations in steroid metabolites – nearly all measured metabolites were significantly correlated within the twin-pairs. In the concordant twin-pairs all but three (92%) were significantly correlated (30 metabolites correlated highly significant with p<0.01, and three significantly; p≤0.05). In the discordant group, 28 out of 36 metabolites (78%) were significantly correlated (27 highly significant; p<0.01, one significantly; p≤0.05). In the concordant group with birth-weight differences of < 1 SDS no significant differences in urinary steroid metabolites were detected. In contrast to this, we found significant intra-twin differences for two DHEAS metabolites in the twins with marked birth-weight differences of more than 1 SDS ("discordant group"): 5-Androstan-3β,16α-diol-17-one (p=0.009, 822.24 vs 737.83 µg/l) and 5-androstan-3β,16α,17β-triol (androstenetriol-16α) (p=0.038, 489.45 vs 437.51 µg/l). All former smaller twins showed higher concentrations of DHEAS-metabolites than their larger co-twins.

Conclusion: In this special group of monozygotic twins with intra-twin birth-weight differences, we could show that birth-weight has a long-lasting impact on steroid profiles. We detected significant differences regarding DHEAS-metabolites with higher concentrations in the former smaller twins and fewer significant intra-twin correlations regarding all metabolites analysed. However, most metabolites analysed in both groups showed highly significant intra-twin correlations, suggesting a major genetic determination of steroid hormone concentrations.

FC9.5**Iodine status of pregnant women and their newborns in the UK – the MABY study**

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Iodine is an essential dietary micronutrient required for thyroid hormone synthesis and neurodevelopment *in utero*. Evidence of iodine insufficiency among British women is of particular concern in the context of pregnancy. The Mothers and Babies at Yorkhill (MABY) study is a Glasgow-based longitudinal cohort study assessing the iodine and thyroid status of pregnant women and their offspring.

Pregnant women were recruited from antenatal clinics (2015–2016) at gestational week (GW) 28+/-1. Maternal blood and urine samples were collected at GW28, GW36; and from both infant and mother in the first week of life. A validated iodine-specific food frequency questionnaire (FFQ) was completed at GW28 and postnatally. Optional maternal hair and breastmilk samples were also collected postnatally. Maternal and infant urinary iodine status (UI) were determined using the Sandell-Kolthoff method.

Pregnant women (n=710) had a median age of 33 (IQR 30–35). Iodine intake at GW28 (100% FFQ completion) was insufficient at 136 µg/day (IQR 101–191); or 199 µg/day (IQR 121–274) including iodine-containing supplements (used by 40%). At GW28, urine and blood samples were collected from 94% & 94% of participants, and 83% & 78% at GW36, respectively. A total of 609 women gave birth and were followed-up (4% dropout, 5% loss at follow-up, 5% exclusion: early delivery & health issues) together with their singleton infants (54%F:46%M). Postnatal maternal data collection (n=609) was: 99% FFQ, 95% urine, 98% blood, 53% hair and 36% breastmilk. Birthweight was 3535g (IQR 3242–3848) and gestational age 40.1 weeks (IQR 39.3–41.0). Urine and blood spots were obtained from 76% and 89% of infants. Maternal UI was 121 µg/L (IQR 61–206) at GW28 (n= 574); 121 µg/L (IQR 62–201) at GW36 (n=503), and 77 µg/L (IQR 32–166) postnatally (n=580), indicative of iodine insufficiency. Neonatal UI (n=463) was 118 µg/L (IQR 71–201), with 65% of infants breastfed, 21% formula-fed, and 14% mixed-fed at 5-days of life.

In this population, only 34% of women met the WHO recommendation for iodine intake at GW28, according to FFQ data (food plus supplement intake). Based on maternal UI, the population is iodine insufficient, with only 42% (GW28) and 41% (GW36) above the 150 µg/L WHO pregnancy sufficiency threshold. By contrast, UI was over the 100 µg/L sufficiency threshold in 59% of infants five days postpartum, indicating preferential mother-to-infant iodine transport. Public health strategies are required to counteract iodine insufficiency during pregnancy and should include focus on improving maternal iodine intake during the prenatal period.

FC9.6**[18F]F-DOPA-PET/MRI or /CT in children with congenital hyperinsulinism**

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Congenital hyperinsulinism (CHI) is a complex heterogeneous disease affecting 1 in 40.000 newborns. Recurrent hypoglycaemia led to permanent mental and motor disabilities in 30–40% of children. Histologically three types had been differentiated: focal, diffuse and atypical. Up to now, only focal-type CHI can be permanently cured by focus removal. Focal-type CHI is characterized by paternal inherited mutation of ABCC8 or KCNJ11 mutations. Therefore mutation analysis of both components of sulfonylurea channel gene is considered standard of care. Localization diagnosis is recommended in all cases with mutation-positive results. In 2003 Otonkoski et al. described [18F]F-DOPA-PET as an accurate method to detect pancreatic hyperfunctioning focal area. Further modifications using hybrid technology of [18F]F-DOPA-PET-CT were developed and a high sensitivity had been described by expert centers. In our cohort of 230 children with congenital hyperinsulinism we suspected focal-type CHI after detection of an isolated paternal transmitted mutation in ABCC8 or KCNJ11 gene. Pancreatic surgery was performed in 86 children to electively remove the hyperfunctioning focus and 25 children with non-focal CHI not responsive to drug therapy. In this series of 111 histology-proven CHI patients we found a sensitivity of 0.97, specificity of 1.0 and positive predictive value (PPV) of 1.0. Negative predictive value (NPV) was 0.88. Since 2015 our collaborative alliance for congenital hyperinsulinism (COACH) further advanced the [18F]F-DOPA technology using [18F]F-DOPA-PET/MRI. 30 patients characterized by isolated paternal transmitted mutation in ABCC8 or KCNJ11 gene were investigated by [18F]F-DOPA-PET/MRI. Histologically a focus was proven in all children and postoperatively euglycemic without need of further treatment. In conclusion, [18F]F-DOPA-PET/MRI is highly recommended for CHI focus localization: (1) with high sensitivity in focus localization, (2) reduced radiation and (3) visibility of sensitive structures including pancreatic duct for guidance of pancreas surgery.

Sex Differentiation, Gonads and Gynaecology or Sex Endocrinology

FC10.1

Investigating the roles of androgens in male reproductive development, maintenance and function by characterisation of androgen and cortisol deficient 11 β -hydroxylase mutant zebrafish lines

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The zebrafish is established as an important model system for studying development and disease, and characterisation of the developmental and functional roles of steroids is crucial for its effective employment in this remit. Whilst oestrogens are known to be essential for female development in zebrafish, the roles of androgens in the development, maintenance and function of the male reproductive system remain unclear.

In order to investigate these processes, we have developed novel zebrafish lines carrying deletions in the gene *cyp11c1*, the zebrafish homologue of *CYP11B1* (11 β -hydroxylase). As in mammals, 11 β -hydroxylase is crucial for production of cortisol, however, in zebrafish this enzyme also plays a crucial role in androgen biosynthesis. Zebrafish larvae deficient in glucocorticoid signalling exhibit an impaired visual background adaption – they are unable to rapidly adjust pigmentation in response to changes in light conditions. *Cyp11c1* mutant zebrafish larvae exhibit impaired visual background adaptation, as well as reduced expression of glucocorticoid responsive genes *fkbp5* and *pck1*, indicating successful disruption of steroidogenesis in our mutant lines.

Adult *cyp11c1* mutant zebrafish may possess either testes or ovaries, this is in agreement with our previous studies which have shown that androgens are dispensable, or only required at very low concentrations, for testes differentiation in this species. Male *cyp11c1* mutant zebrafish exhibit primarily female secondary sex characteristics and are infertile when crossed with a wild-type female. Analysis of mating behaviour has revealed that *cyp11c1* mutant male zebrafish exhibit decreased stereotypic breeding behaviours when crossed with a wild-type female, compared to wild-type siblings. This indicates that androgens may be important regulators of sexual behaviour in zebrafish.

Histological examination of the testes of *cyp11c1* mutant zebrafish revealed a disorganised structure with smaller and less defined seminiferous tubules. Although all stages of spermatogenesis were represented in the testes of *cyp11c1* mutant zebrafish, the number of mature spermatozoa appeared to be reduced whereas earlier generations appeared to be more abundant than in wild-type siblings. Further histological investigation of the reproductive tract revealed a severely hypoplastic spermatic duct in *cyp11c1* mutant zebrafish. Semen release was severely impaired in *cyp11c1*

mutant zebrafish, probably as a result of spermatic duct malformation. In addition, semen collected from *cyp11c1* mutants contained significantly fewer sperm than wild-type siblings.

Cyp11c1 mutant zebrafish appear to be more androgen deficient than previously described lines, and represent an exciting opportunity to gain further insight into the roles of androgens in male reproductive development, function and behaviour.

FC10.2

The Fruit Fly, *Drosophila melanogaster*, as a model to elucidate human differences of sex development (DSD)

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Background: An activation cascade of specific genes sets up the initiation of sex determination leading in males to testes formation and synthesis of testicular hormones. Disruption of this gene cascade may cause a spectrum of disorders/differences of sex development (DSD) phenotypes. Here we describe for the first time two sisters suffering from 46,XY DSD, who by whole exome sequencing were shown to carry a mutation in the X-linked StAR-related lipid transfer domain protein 8 (STARD8) gene. STARD8, also known as deleted in liver cancer 3 (DLC-3) is a functional Rho-specific GAP protein, the loss of which enhances perinuclear Ras homolog gene family member A (RhoA) activity which in turn is known to be involved in SOX9 expression regulation. Additionally, STARD8 downregulation severely disturbs recruitment of β -catenin to sites of cell adhesion, this one being, moreover, a key pro-ovarian and anti-testis signalling molecule.

Objectives: To gain new insights in human sex development mechanisms, we aimed to analyze the functional consequences of STARD8 mutations. Since the STARD8 knockout NMRI mouse model we generated did not recapitulate the human clinical picture, we chose to use another *in vivo* model to study the mechanisms of disease. Interestingly, *Crossveinless-c* (*Cv-c*) the *Drosophila* homolog of DLC-3/STARD8, has similar location and function than its mammalian counterpart. We therefore chose to study the consequences of *Cv-c* mutations in the gonadal development of the fruit fly.

Methods: Gonad development was analyzed in *cv-c⁷*, *cv-c^{M62}* and *cv-c^{C524}* alleles using Immunohistochemistry and confocal microscopy to visualize gonad specifics markers. *Cv-c* expression in the male gonad was confirmed by *cv-c* fluorescent RNA *in situ* and *Cv-c*-GFP TRAP construct.

Results: We found defects affecting the germ cells (GCs) migration from the beginning of embryogenesis with different degrees of severity in the *cv-c* mutant embryos, preventing gonad coalescence in the most severe cases. We also observed a decrease in the number of GCs in male mutant gonads compared to wild type males.

Conclusions: Our results indicate that *cv-c* is required for gonadal development in *Drosophila* embryos, suggesting that the defect in STARD8 is the most likely cause of DSD in our patients. We were able to exploit the fruit fly, *Drosophila melanogaster*, for functional investigation of findings from human whole exome sequencing, by creating a fly model of a defect in the protein STARD8 found in two patients with 46, XY DSD.

FC10.3

Mutations in the DEAH-box RNA Helicase DHX37 are a frequent cause of 46,XY gonadal dysgenesis and 46,XY testicular regression syndrome

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XY individuals with Disorders/Differences of Sex development (DSD) are characterized by reduced androgenization caused, in some children, by gonadal dysgenesis or, more rarely, testis regression during early fetal development. The genetic etiology for most patients with 46,XY gonadal dysgenesis and for all patients with testicular regression syndrome (TRS) is unknown. Identification of novel genes involved in DSD is crucial for providing an accurate clinical diagnosis, aiding patient management and understanding the biological processes involved. We performed exome and/or Sanger sequencing in 145 individuals with 46,XY DSD of unknown etiology gonadal dysgenesis (n=81), TRS (n=16), boys with penoscrotal hypospadias (n=33) or anorchia (n=15). Thirteen children carried heterozygous missense mutations involving the RNA helicase DHX37, which is essential for ribosome biogenesis in yeast. Enrichment of rare/novel DHX37 missense mutations in 46,XY DSD is highly significant compared to controls (*P* value = 5.8×10^{-10}). Five mutations are *de novo* (*P* value = 1.5×10^{-5}). Twelve mutations are grouped in two highly conserved functional domains and are predicted to disrupt biological function. Mutations were specifically associated with gonadal dysgenesis (9/81, 11%) and TRS (4/16, 25%). Consistent with a role in early testis

development, DHX37 is expressed specifically in somatic cells of the developing human and mouse testis. DHX37 mutations are a relatively common cause of an autosomal dominant form of 46,XY DSD, which includes both gonadal dysgenesis and TRS, showing that these conditions are part of a clinical spectrum. This raises the possibility that some forms of DSD may be a ribosomopathy.

FC10.4

Loss-of-function and missense mutations in MYRF are a novel cause of autosomal dominant 46,XY Leydig cell hypoplasia and 46,XY gonadal dysgenesis

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MYRF is known to regulate the myelination of the central nervous system and mice with a conditional deletion of *MYRF* in oligodendrocyte precursors has anomalies of motor skill. Recently, several loss-of-function and missense mutations in *MYRF* have been reported in association with syndromic forms of congenital heart disease (CHD) with elements of Scimitar syndrome and/or with congenital diaphragmatic hernia (CDH). In most 46,XY individuals a range of urogenital anomalies were reported.

In an exome screen of 240 individuals with 46,XY DSD we identified three children with loss-of-function mutations in *MYRF* and one individual with a novel, predicted deleterious, missense mutation. The first case consisted of a 46,XY female who presented with primary amenorrhea at 14 yrs with female external genitalia, uterus and gonads located in the pelvis. Gonadotropins were elevated and testosterone levels were low. She was diagnosed with 46,XY partial gonadal dysgenesis. She carried a novel loss-of-function mutation involving an essential splice site c.2572+1G>A in *MYRF*. The second case consisted of a 46,XY boy with ambiguous external genitalia and hypogonadism. Histology of the gonads indicated a testis-like structure with absence of Leydig cells suggesting Leydig cell hypoplasia. He carried a novel missense mutation c.A313G:p.N105D in *MYRF* that was predicted to be damaging to the protein by multiple predictive software. A third child, who presented at birth with ambiguous external genitalia and inguinal testis and was raised as a female. The karyotype was 46,XY. Histology of both the left and right testis revealed tubule structures with Sertoli cells but with the complete absence of Leydig cells indicating Leydig cell hypoplasia. Exome sequencing revealed a *de novo* frameshift mutation c.2831_2835del:p.N944fs*51 in *MYRF*. The fourth case was a 46,XY girl who presented at birth with ambiguity of the external genitalia, minor cardiac anomalies and CDH. Histology of the gonads indicated Leydig cell hypoplasia. Exome sequencing revealed a *de novo* frameshift mutation c.2270delG:p.S725fs*64.

All four mutations are absent from public databases including gnomAD and in two of the children, where DNA of the parents was available for study, the mutation was found to be present only

in the affected child. In three of the four children, there was no evidence of any other somatic anomalies. These data indicate that mutations in MYRF are associated with both syndromic and non-syndromic forms of 46,XY partial gonadal dysgenesis and 46,XY Leydig cell hypoplasia.

FC10.5

Transcriptome analysis of novel Sertoli cell models to highlight potential genes involved in DSD mechanism of disease

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Background: Determination of the gonads in men is closely dependent on Sertoli cells differentiation and maturation. Many cases of differences of sex development (DSD) are caused by variations in these processes. The study of the mechanisms underlying these complex conditions is crucial for optimal clinical management and Sertoli cells would be an ideal model for this purpose. Our human Sertoli-like cell model (SLCs) may shed some light on the identification of new genes and common pathways involved in the mechanism of disease in DSD.

Objective and Hypothesis: To explore the transcriptomes of three Sertoli cell models Ntera2 (NT2d1), primary human Sertoli cells (HSerCs) and the new SLCs in order to find significant expression differences and similarities that prove the quality of SLCs as a human Sertoli cell model and highlight new potential genes involved in the development of human Sertoli cells.

Methods: We used RNA-Sequencing to analyze the transcriptome of NT2d1, HSerCs and SLCs. Gene Ontology (GO) enrichment of the significantly regulated genes ($p<0.05$, $FC>=2$) in NT2/D1, HSerC and SLCs, compared to induced pluripotential stem cells (iPSCs) using ToppCluster. Similarities and differences in the transcriptome of the three Sertoli-like cell lines were visualized using Cytoscape.

Results: This approach revealed that SLCs and HSerCs are much more similar among each other (37 upregulated genes in common) than NT2d1 cells (only 3 upregulated genes in common). We observed that SLCs and HSerCs significantly expressed PAX2 and Hox gene complex from the Homeobox family, a renowned sub-family of genes expressed in both fetal and adult reproductive organs. Both Pax2 and Hox genes are linked to multiple steps of urogenital development and bipotential gonad formation. The functional redundancy among members of this large family may be masking a role in sex developmental defects. Of special interest is the observed significant upregulation of TBX18, (member of the T-box family), with some members of this family forming a complex with HOX proteins to initiate Sf1 gene expression during adrenal development.

Conclusion: Sertoli-like cells have proved to be a better model than the commonly used NT2d1 cells to study human Sertoli cells. Moreover, the comparison of high-quality Sertoli cell models highlighted several common genes that may conceal a not yet known role in male gonadal development.

FC10.6

Evaluation of basal and gnrh-stimulated AMH levels in central precocious puberty, peripheral precocious puberty and premature thelarche

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Objective: AMH decreases by 30% in the first two years following puberty. Although it is known that AMH is associated with FSH and LH, the AMH response to rapid changes in GnRH is not known clearly in puberty. It has been shown that AMH levels in central precocious puberty (CPP) are lower than in premature thelarche (PT), but the levels of AMH in peripheral precocious puberty (PPP) have not been evaluated. The aim of this study was to evaluate the basal and stimulated AMH levels in CPP, PPP and PT groups.

Materials and Methods: Patients who had breast development before 8 years old and had undergone GnRH test were included in the study. Blood samples were taken at 0th, 45th and 90th minute of GnRH test from 73 patients. Patients were grouped as SPP, PPP and PT according to clinical and laboratory findings.

Results: The median age of patients was 7.8 (4.1-9.3) years. Of the patients, 43.8% (n: 32) were CPP, 42.5% (n:31) were PT, 13.7% (n:10) were PPP. The median basal AMH levels in the PPP, CPP and PT group were 0.09 ng/ml (0.05-0.31), 0.19 ng/ml (0.05-0.56) and 0.29 ng/ml (0.07-0.77) respectively. There were statistically significant differences in the basal AMH levels between three groups ($p:0.0001$). The stimulated AMH level was significantly higher than the baseline ($p:0.0001$). In the 32.9% (n:24) of patients, peak FSH levels were reached in 45th minutes, however in the 74% (n:54) of patients peak AMH levels were reached in 45th minutes at GnRH test. The stimulated/basal AMH levels were significantly different in three groups ($p:0.002$). The median stimulated/basal AMH ratios in PPP, CPP and PT group were 12.2 (5.7-30.6), 8.9 (2-39.3) and 6.5 (2.3-18.3) respectively. The cut-off value of the stimulated/basal AMH ratio, to differentiate PP group (SPP+PPP) from the PT group, was found to be 6.57 with a sensitivity of 79% and a specificity of 52% (AUC:0.703 p:0.003).

Conclusion: In this study, which examined for the first time the AMH response to GnRH stimulation in puberty, it was found that AMH was significantly increased with GnRH stimulation and AMH was peaked at 45 minutes in ¾ of subjects. It was found that the stimulated/basal AMH ratio was the highest in the PPP group with the lowest basal AMH level; and was the lowest ratio in the PT group with highest basal AMH level.

Pituitary, Neuroendocrinology and Puberty Session 2

FC11.1

Phenotypic characterization of a large pediatric cohort of patients with genetic forms of congenital hypopituitarism

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Background: Genetic variants are identified in a small proportion (~10%) of patients with Congenital Hypopituitarism (CH), with variable associated phenotypes. We aimed to phenotypically characterise a large cohort of patients with genetically proven CH.

Patients and Methods: 1684 CH patients were screened (Sanger or whole exome sequencing) over a 20-year period (1998–2018) for mutations in genes regulating pituitary development. The cohort included patients with: Multiple Pituitary Hormone Deficiency (MPHD) (n=621), Isolated Growth Hormone Deficiency (IGHD) (n=414), Holoprosencephaly (HPE) (n=64), Septo-Optic Dysplasia (SOD) (n=526) and Severe Eye Defects (SED) (n=59). Retrospective clinical/neuroradiological data were collected.

Results: Genetic variants were identified in 146/1684 patients (8.7%): 54/621 (8.7%) MPHD, 59/414 (14.3%) IGHD, 3/64 (4.7%) HPE, 14/526 (2.7%) SOD, 16/59 (27.1%) SED. The most frequent genetic variants identified in different groups were: *PROPI* and *POU1F1/PIT1* for MPHD; *GH1*, *GHRHR* and *GLI2* for IGHD; *PROKR2* for SOD; *SOX2* for SED; and *SHH* for HPE. Pituitary deficits were present in 140/146 (95.9%) patients. The majority had GHD, except for *SOX2* mutations (isolated gonadotrophin deficiency). Other pituitary deficiencies were more variable. Stimulated peak GH concentrations were lowest in those patients with *POU1F1/PIT1* ($0.30 \pm 0.21 \mu\text{g/L}$), *LHX3* ($0.71 \pm 0.53 \mu\text{g/L}$), *GHRHR* ($0.73 \pm 0.76 \mu\text{g/L}$), *PROPI* ($0.80 \pm 0.79 \mu\text{g/L}$), and *SOX3* ($0.88 \pm 1.03 \mu\text{g/L}$) mutations. Hypothalamo-pituitary abnormalities were reported on MRI in 98/124 (79%) patients, the most prevalent being a small anterior pituitary across all groups. 4/15 (26.7%) patients with *PROPI* and 1/2 patients with an *FGF8* mutation had anterior pituitary enlargement; ectopic posterior pituitary was detected in 6/11 (54.5%) *PROKR2*, 3/8 (37.5%) *GLI2*, 4/5 (80%) *SOX3*, 3/6 (50%) *HESX1*, 3/4 (75%) *LHX4* and 4/4 (100%) *OTX2* variants.

Midline forebrain developmental defects were associated with *PROKR2*, *FGF8*, *KAL1*, *TCF7L1*, *SOX2*, and *SHH* mutations, whilst other brain abnormalities (eg. hippocampal/cerebellar abnormalities, hypothalamic hamartoma) were identified in patients with *SOX2*, *PROKR2*, *OTX2*, *GH1*, *SOX3*, *FGF8* variants. Neurological abnormalities (developmental delay, autistic spectrum disorder, epilepsy) were prevalent in patients with *SOX2*, *PROKR2*, *OTX2*,

SHH, *TCF7L1*, *FGF8*, and *LHX3* variants. Skeletal malformations and deafness were described in all patients with an *LHX3* mutation, whilst eye defects were present in all patients with *SOX2* variants.

Conclusions: Heterogeneous phenotypes are associated with CH. However distinctive hypothalamo-pituitary and extra-pituitary features in these patients can aid in genotype prediction. Due to the rapidly increasing number of hypothalamo-pituitary associated genes, next generation sequencing has replaced Sanger sequencing enabling a fast and thorough analysis of patient genomes to identify novel mutations and candidate genes.

FC11.2

A novel minor spliceosome defect associated with growth hormone deficiency (GHD) and primary ovarian insufficiency (POI)

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Objectives: We describe 5 pedigrees with a novel phenotype including GHD associated with primary ovarian insufficiency (POI) and investigate the underlying molecular basis.

Patients and Methods: 6 Turkish patients (5F, 1M) born to 5 consanguineous pedigrees with severe GHD were identified. All females had POI; the male had normal puberty. All had severe postnatal growth retardation (height -4.4 to -8.9 SDS at presentation) with clinical GHD, low normal prolactin concentrations (0.2–4.6 ng/ml), undetectable basal IGF-I and IGFBP-3, and absent GH responses to provocation. Brain MRI showed anterior pituitary hypoplasia. Serum FSH was elevated in the eldest girl (FSH 24.8 U/L, LH 0.7 U/L) at age 8 years. Spontaneous puberty ensued at age 14 years (FSH 86.6 U/L, LH 32.1 U/L), but arrested at Tanner stage 3 with undetectable oestrogen. The other four affected females had elevated gonadotropins from age 3 years. Pelvic ultrasonography/MRI showed a small uterus along with small/undetectable ovaries in all girls. We performed whole exome sequencing (WES) on 6 affected patients and one unaffected parent. Expression of Rnpc3/RNPC3 was analysed by in situ hybridization on murine/human embryonic sections. RT-PCR was used to test splicing efficiency. Crispr/Cas9 was used to generate mice carrying the p.L483F mutation in the conserved murine Rnpc3 RRM2 domain.

Results: All affected patients present a novel homozygous missense variant (p.L483F) in RNPC3 (unaffected father heterozygous). RNPC3 encodes a 65K protein component of the U12-type spliceosome and required for U11/U12 small nuclear ribonucleoprotein (snRNP) formation and U12-type introns splicing. RNPC3 mutations were previously described in isolated GHD patients (Argente J et al., Embo Mol Med 2014). Abnormal U12 in-

tron processing of preprohormone convertases SPCS2 and SPCS3 and actin-related ARPC5L genes (GH dysfunction candidates) and NUP107 (female-specific gonadal dysgenesis candidate) was observed in patient fibroblasts compared to controls. In both mouse and human, Rnpc3/RNPC3 was expressed in the telencephalon, diencephalon, trigeminal ganglia, hypothalamus and Rathke's pouch. Female homozygous mutant mice displayed a 20% reduction in pituitary GH content ($p=0.016$). Histological examination of sexually mature ovaries revealed no abnormalities.

Conclusion: A novel homozygous missense mutation (p.L483F) in RNPC3 was associated with GHD in humans and mice. Female human patients also present ovarian dysgenesis, in keeping with elevated FSH concentrations in previous patients (1). Our findings provide novel insights into the role of RNPC3 in ovarian function and emphasize a critical role of minor spliceosome in the processing of genes required for pituitary and ovarian development and function.

FC11.3

A novel genetic aetiology for familial neonatal central diabetes insipidus

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Background: Central diabetes insipidus (CDI) in the neonatal age is usually a result of intracranial insult, either congenital or acquired. Familial CDI is usually an autosomal dominant disorder, presenting later in childhood (1-6 y) with polyuria and mostly caused by mutations in the Neurophysin II moiety of the AVP-NPII prohormone gene; these interfere with prohormone processing leading to gradual destruction of AVP secreting cells and result in arginine vasopressin (AVP) deficiency.

Objective: To assess the clinical, biochemical, and the genetic etiology of an unusual clinical presentation with neonatal CDI.

Clinical Course: A 5 days old girl born to asymptomatic parents presented with severe dehydration, polyuria of 6-8 ml/kg/h, polydipsia, hypernatremia of 161 mmol/l, serum hyperosmolality of 322 mOsm/kg with concomitant low urine osmolality of 200 mOsm/kg. Normal serum sodium levels and osmolarity were achieved by 8 mg/d/Kg of desmopressin administered orally. Pituitary hormones levels and Magnetic resonance imaging (MRI) were normal.

Sequencing of the AVP-NPII gene performed given the neonatal presentation and the possibility of consanguinity between parents revealed no mutations. Whole exome next generation sequencing revealed a homozygous splicing exon12:c.955-9C>A mutation in the neuroblastoma-amplified sequence - NBAS gene which is highly expressed in the pituitary gland and so far known to be associated with Short Stature, Optic Nerve Atrophy, and Pelger-Huet Anomaly. The mutation is predicted to alter significantly the splicing and is not present in a population cohort from the relevant ethnic background.

As ER-associated degradation has been recently reported to be required for vasopressin prohormone processing it is not surprising that a mutation in NBAS gene causes CDI as NBAS mainly functions as a component of an endoplasmic reticulum (ER) tethering complex.

Conclusion: The novel c.955-9C>A mutation in the ER tethering complex gene NBAS is probably a new genetic etiology for CDI. The unique neonatal clinical presentation suggests a special and early role for NBAS protein in the neonatal synthesis of AVP. Splicing and functional studies are currently underway.

Reference

- Guojun Shi, Martin Spiess, Ling Qi; ER-associated degradation is required for vasopressin prohormone processing and systemic water homeostasis; *J Clin Invest.* 2017;127(10):3897-3912.

FC11.4

Whole exome sequencing in a familial case of adamantinomatous craniopharyngioma revealed two hits affecting Wnt-signaling pathway

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Background: Craniopharyngiomas (CPs) are benign brain tumors that intimately involve pituitary and, often, hypothalamus. Here, primary clinical conundrum is choosing between gross total resection and preserving endocrine functions. Robust predictors of recurrence are much needed, but require a deeper understanding of the molecular basis of CPs. Multiple studies show that CTNNB1 (β -catenin) somatic mutations drive the adamantinomatous subtype (adaCP). However, many adaCPs feature intact CTNNB1, suggesting that these tumors may also arise from other defects in the Wnt signaling pathway. In this study, we present a familial case of adaCP revealing a second-hit somatic mutation in APC—a widely recognized regulator of the Wnt-signaling pathway, where β -catenin is the primary effector.

Subjects & Methods: We studied a family with two maternal half-sisters (current age, 19 and 26 years) who underwent surgery for CP at the age of 14 and 15 years, respectively. We obtained blood samples from both siblings, their mother and father of the younger child (proband), as well as fresh frozen tumor samples from the proband. Whole exome sequencing of these samples was performed on Illumina NextSeq platform. The regions with mutations of interest were additionally analyzed by Sanger sequencing.

Results: Three family members (both siblings and their mother) share a novel heterozygous germline c.7455_7458delTCCT:p.S2487FfsX28 variant in APC gene. This variant is predicted to disrupt C-terminal domains binding microtubule-associated pro-

teins EB1 and DLG. In proband, whole exome sequencing of the tumor sample showed intact *CTNNB1*; however, we discovered another variant in *APC* gene (c.904C>T:p.R302X). R302X variant is reportedly associated with familial adenomatous polyposis (FAP) and results in a loss of all APC domains required for β -catenin inactivation. Additional studies using TA cloning and Sanger sequencing of GRCh37/hg19_chr5:112151102-112154104 region encompassing c.904C position and polymorphic variant rs12656359 confirmed that the somatic mutation occurred on paternal allele. Histological evaluation of FFPE specimens confirmed adaCP in both children.

Conclusion: To our knowledge, this is the first evidence to show that mutations in *APC* may recapitulate classic clinical and histological features of an adaCP in the presence of intact *CTNNB1* gene.

FC11.5

Survival, endocrine disorders and quality of life in 135 children with craniopharyngioma after surgical or combined treatment

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Patients and Methods: We analyzed 135 primary operated craniopharyngioma (CP) patients and 75 CP patients, received radiotherapy/radiosurgery in 2005-2012. Neurologic, endocrine, visual functions, quality of life (QoL) and neuroimaging data before and after treatment were assessed.

Patients were divided in 2 groups according to CP location: 48,5% endosellar (ESCP), and 51,5% suprasellar (SSCP). Surgical treatment included tumor excision (total in 34,9%, subtotal in 25,7%, and partial in 24,8% cases), transnasal cyst evacuation in 10,1%, Omaya implantation in 4,5%.

Results: 5-year PFS after total resection was 79%, it was significantly ($p<0.01$) higher than after nonradical resection - 20% (after subtotal resection 4%, partial resection 37%, transnasal cyst aspiration 27%, and Omaya implantation 0%). 5-year PFS after subtotal or partial tumor resection followed by irradiation was 86% - similar as after radical tumor excision.

Endocrine function depended from tumor location. Patients with ESCP had more prominent pituitary deficiency before surgery (20% panhypopituitarism), than patients with SSCP (4.5% panhypopituitarism). Tumor resection caused endocrine status deterioration: 80% after surgery had panhypopituitarism and diabetes insipidus (DI).

Anterior pituitary deterioration significantly more often occurred after total tumor resection ($p<0.01$), than after other surgical procedures. DI occurred after total resection more often too, though it was not significant ($p=0.07$). The incidence of new hormone deficit after subtotal, partial resection or after transnasal cyst evacuation didn't differ. There was no endocrine deterioration after Omaya implantation.

15/75 patients before radiation had partially preserved anterior pituitary function. Surprisingly, but only in 1/15 cases irradiation induced new hormone deficit – adrenal insufficiency 3.5 years after irradiation.

QoL score didn't correlate with sex, height SDS, DI, anterior pituitary hormone deficiency, or visual function. There was significant correlation between QoL score and age at surgery ($R=0.4$, $p<0.01$), and QoL score and BMI SDS ($R= -0.3$, $p=0.001$). BMI SDS slightly increased after ESCP excision (from -0.1 to 0,3, difference is NS). In patients with SSCP BMI SDS significantly increased after total resection (from 0.06 to 1.6, $p<0.001$), and subtotal resection (from 0.5 to 1.5, $p=0.005$), and not significantly increased after partial resection or Omaya implantation (from 0.5 to 1.0, $p=0.3$). In SSCP group QoL score was significantly higher after partial resection/Omaya followed by irradiation, than after total resection ($p=0.01$)

Conclusion: Optimal treatment for patients with ESCP with panhypopituitarism before surgery is total tumor excision. The optimal management of SSCP with risk of hypothalamic involvement is limited surgery, followed by irradiation.

FC11.6

Pubertal timing in parents is associated with timing of pubertal milestones in offspring of concordant sex – but only inconsistently with milestones in offspring of discordant sex

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Context: Puberty timing is highly heritable. Recent genome-wide association studies, comparing timing of menarche in girls to timing of voice-break and facial hair in boys, revealed a largely overlapping genetic architecture of female and male pubertal timing. However, it is also known that genetic heterogeneity between sexes exists for some loci.

Objectives: We hypothesized that self-reported relative parental pubertal timing is associated with timing of pubertal milestones in offspring of concordant sex – but that associations may diverge in offspring of discordant sex.

Participants & Methods: Population-based mixed cross-sectional and longitudinal cohort of 1381 healthy children (821 girls and 560 boys; COPENHAGEN Puberty Study; cross-sectional: n=1244, longitudinal: n=137) that underwent blood sampling including measurement of reproductive hormones and clinical examinations including assessment of four/five pubertal milestones in girls/boys, respectively. Their parents answered a questionnaire on their relative (early/average/late) pubertal timing and age at menarche.

Results: We observed significant associations of relative parental pubertal timing with timing of all pubertal milestones in offspring of concordant sex, i.e. fathers/sons (e.g. testicular enlargement ≥ 4 mL: $p=0.004$, $\beta = 0.34$ (SE: 0.10) years per relative category) and mothers/daughters (e.g. thelarche: $p<0.001$, $\beta = 0.45$ (SE: 0.10) years per relative category). Age at menarche in mothers was associated with all pubertal milestones in girls, except axillary

hair growth. Concerning pubertal timing in offspring of discordant sex, i.e. mother/sons and father/daughter, the results were more heterogeneous. While relative pubertal timing in fathers was significantly associated with timing of pubarche and menarche ($p=0.03$ and 0.01 , respectively) in girls, it was not associated with thelarche or axillary hair growth. Relative pubertal timing in mothers was significantly associated with timing of testicular enlargement, pubarche and voice-break in boys ($p=0.002$, 0.001 and 0.001 , respectively), but not with sweat odor or axillary hair growth. Self-reported age at menarche in mothers was associated with all pubertal milestones in boys, except sweat odor. We further tested hormonal outcomes, i.e. Testosterone above limit of detection ($>0.23\text{nmol/L}$) in boys and Luteinizing Hormone $>0.3\text{IU/L}$ in girls, and observed a similar pattern of significant associations in concordant sex and no association in discordant sex.

Conclusion: We demonstrate that self-reported pubertal timing in parents is consistently associated with timing of pubertal milestones in offspring of concordant sex but only inconsistently with milestones in discordant sex pointing to a distinct heterogeneity in the genetic architecture of timing of pubertal milestones between sexes.

Growth and Syndromes (to Include Turner Syndrome)

FC12.1

Increasing knowledge in IGF1R defects: lessons from 20 new patients

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Background: IGF1R is a keystone of foetal growth regulation by mediating the effects of both IGF-I and IGF-II. Recently the first clinical cohort of patients carrying an *IGF1R* defect has been reported from which a clinical score was established for diagnosis. Since no external validation of this score is available we assessed it in a large cohort of patients with identified *IGF1R* defects. Furthermore we aim at setting-up a functional test to allow classification of unknown significance variants *in vitro*.

Methods: DNA was tested for either deletions or point mutations. By western blot and from fibroblasts of nine patients, we studied the phosphorylation of downstream pathways after stimulation with IGF-I.

Results: Twenty-one *IGF1R* independent defects were detected in 35 patients, including eight deletions and 10 heterozygous, one homozygous and one compound heterozygous variants. Main clinical characteristics of these patients were being born small for gestational age (90.9%), adult short stature (78.3%) and

microcephaly (74.1%). Feeding difficulties and variable degrees of developmental delay were highly prevalent (54.5%). No difference in phenotypes was observed between patients with deletions or mutations of *IGF1R*. Functional studies showed that the six missense variants that were tested were associated with a decreased in AKT phosphorylation.

Conclusion: We report eight new pathogenic variants in *IGF1R* and an original case with a homozygous variant. We demonstrated that the recently proposed clinical score was accurate for the diagnosis of *IGF1R* defects. We developed an efficient functional test to assess pathogenicity of such variants, which is useful especially for those variants with unknown significance.

FC12.2

NPR2 gene mutations were found in 5.4% children with familial short stature

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Introduction: C-type natriuretic peptide receptor encoded by *NPR2* gene stimulates chondrocyte differentiation and hypertrophy and extracellular matrix production within the growth plate. The phenotypical spectrum of *NPR2* mutations is broad, from severe autosomal recessive acromesomelic dysplasia to milder autosomal dominant growth disorders. Some children with *NPR2* variants are treated with growth hormone (GH), however, with the inconsistent results.

Aims: To elucidate the frequency of pathogenic *NPR2* gene variants among children with familial short stature (FSS) and to describe their phenotype in detail including the GH treatment response.

Materials and Methods: A total of 112 children with FSS out of 917 children registered in the single center database of patients treated with short stature who met inclusion criteria: body height (BH) before GH therapy ≤ -2 SD in both patient and shorter parent and with unknown genetic etiology of short stature, were included in our study. The Next generation sequencing methods were performed searching for *NPR2* gene variants. The results were evaluated using ACMG standards and guidelines. The phenotype of children with (likely) pathogenic variants was described including the GH treatment response (growth velocity, body-height SDS increase over five years of treatment).

Results: In total of 6 children (from 5 families) out of 112 children with FSS (5.4%), the (likely) pathogenic variant in *NPR2* gene was found [p.Ile558Thr (in three), p.Arg205*, p.Arg557His, p.Ser603Thr]. The mean birth weight and length of affected children was -1.2 SD ($+0.9$ to -2.0) and -1.9 SD (-1.2 to -3.1) respectively. Three of them were born small for gestational age (SGA). The BH before GH therapy was -3.3 SD (mean, range -2.6 to -4.0) in all affected children and -2.7 SD (-2.1 to -3.7) in their shorter parents. Mean IGF1 level was -1.5 SD (-1.4 to -1.7), maximal stimulated

GH concentration was 9.6 ug/l (4.5-17.0) in all affected children. Three of them were clinically classified as GH deficient. Five out of six children with *NPR2* gene variants were treated with GH. The mean age of treatment initiation was 6.5 years, mean GH dose 0.034 mg/kg/day (0.031 to 0.038). The growth velocity after GH treatment initiation improved from 5.1 to 8.7 cm/year ($p=0.0003$, paired sample T-test). The height SDS increased from -3.3 to -2.1 over five years of treatment ($p<0.001$, linear mixed-effects model).

Conclusion: *NPR2* gene variants cause a substantial part of FSS. The GH therapy should be considered in children carrying *NPR2* gene variants.

FC12.3

Growth hormone treatment in adults with Prader-Willi syndrome has sustained positive effects on body composition

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Context: In children with Prader-Willi syndrome (PWS), the benefits of growth hormone (GH) treatment are well established. Currently, when young adults with PWS have attained adult height (AH), they have to stop GH treatment. Several one year studies have shown that GH treatment is also beneficial for adults with PWS, improving body composition. However, little is known about the longer-term effects.

Objective: To investigate the effect of either continuation of GH for 2 years after AH attainment or restart of GH for 2 years after cessation for a median period of 1 year on body composition

Design: Open-label, prospective study in 48 young adults with PWS.

Setting: Dutch PWS Reference Center.

Main outcome measures: Fat mass percentage (FM%) SDS and Lean body mass (LBM) SDS, measured by DXA.

Results: In the 22 adults who continued GH after AH attainment, estimated mean (95% CI) FM% SDS did not change during 2 years of GH treatment (2.2 (1.9 to 2.4) SDS at baseline vs. 2.2 (2.0 to 2.4) SDS after 2 years, $p=0.42$), neither did LBM SDS (-2.0 (-2.6 to -1.5) SDS vs. -2.0 (-2.5 to -1.5) SDS, $p=0.94$). In the 26 adults who restarted GH after they had stopped GH for a median duration of 1 year, FM% SDS decreased significantly during 2 years of GH, from 2.2 (2.0 to 2.4) SDS to 1.9 (1.7 to 2.1) SDS, $p<0.001$, while total body LBM SDS increased significantly from -2.3 (-2.7 to -2.0) SDS to -1.9 (-2.2 to -1.5) SDS, $p<0.001$. Estimated mean fasting glucose increased from 4.2 mmol/l at baseline to 4.8 mmol/l after 2 years of GH treatment ($p=0.004$), and insulin from 42.5 pmol/l to 69.5 pmol/l ($p=0.001$), but both remained within normal limits. None of the patients developed type 2 diabetes mellitus. Systolic and diastolic blood pressure did not change during 2 years of GH and were within the normal range in all patients. There were no GH-related adverse events during the study.

Conclusions: Continuation of GH treatment for two years after attainment of AH maintains the positive effects on body composition attained during childhood, while restart of GH after discontinuation for 1 year improves body composition. Thus, adults with PWS benefit from longer-term GH treatment, without major side effects or safety concerns.

FC12.4

Integration of transcriptomic and epigenomic data in childhood identifies a subset of individuals born small for gestational age (SGA) with "catch-up" growth who become pre-hypertensive in early adulthood

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Background: Children born SGA are known to develop cardiometabolic conditions in adulthood¹. Nothing is known about the relationship of the transcriptome (gene expression) and epigenome (DNA methylation) to birth size and the future development of cardiometabolic disease.

Aim: To identify, **I**) differences and functional links between epigenome age-7years, transcriptome age-9years associated and birth size in a normal population; **II**) links between the transcriptome and epigenome in childhood and adult cardiometabolic risk.

Study Design: Normal children (n=6487) from the Avon Longitudinal Study of Parents and Children were assigned to groups based on birth size using bodyweight and gestation and divided into groups using population level 10th and 90th centiles. Adverse cardiometabolic risk at age-17years was defined by the National Heart Lung and Blood Institute criteria of prehypertension using systolic and diastolic blood pressure². Blood epigenome and transcriptome were available from 980 children age-7years and 947 children age-9years respectively. Hypernetworks were used to integrate differentially expressed genes (DEGs) and methylated points (CpGs), identifying functional links. Random Forest, a machine learning approach, was used to determine the predictive value of 'omic data presented as the area under the curve of the receiver operating characteristic (AUC).

Results: Unsupervised analysis identified significant differences between birthweight groups in the whole transcriptome and epigenome (p -value range, $6.6 \times 10^{-16} < p < 1.0 \times 10^{-2}$). Pre-hypertensive participants at age-17years were distinguished from normotensive participants and 'omic differences were defined (232DEGs; $2.0 \times 10^{-6} < p < 1.0 \times 10^{-2}$ & 830CpGs; $1.1 \times 10^{-8} < p < 1.0 \times 10^{-2}$). The pre-hypertensive group was enriched for children born small who caught up by age-7years (155/611 unhealthy/healthy compared to 1979/12746 in the other groups; 1.6-fold, $p < 1 \times 10^{-5}$). This group had a greater height velocity during their catch-up period than the normotensive participants (1.2-fold, $p=0.027$). Hypernetwork integration of 'omic data identified a functional relationship between DEGs at age-9years and CpGs at age-7years (55DEGs, 520CpGs). Identified CpGs grouped into 5 chromosomal regions (corrected- $p < 6.7 \times 10^{-5}$) including the genes *SLC44A2* and *PON1* with known associations to lipid metabolism. Genetic associations are known

between *PON1* and SGA². Random forest analysis was able to accurately predict the presence of pre-hypertension aged 17 from the early life 'omic data (epigenome age-7years AUC:0.982 and transcriptome age-9years AUC:0.973).

Conclusions: We have identified an integrated 'omic signature in childhood which defines a subset of individuals, born small who catch up by age-7years and are at increased risk of later cardio-metabolic disease.

¹ Barker *et al.* (1988) BMJ **297**(6641):134-135.

² Chobanian *et al.* (2003) JAMA **289**(19):2560-2571.

³ Infante-Rivard (2010) Am.J.Epidemiol **171**(9):999-1006.

month of treatment ($p=0.014$). Total growth over the five year study was significantly elevated for Cluster 3 (Clusters 1, 2 and 3; mean growth (cm \pm SD)= 25.7 ± 0.8 , 28.9 ± 3.3 , 31.1 ± 4.3 ; $p=0.04$). Cryptic Y material, not detected by karyotyping, was defined by transcriptomic analysis. eQTL mapping using the 11 SNPs, identified 849 transcriptomic associations ($0.02 > p > 5.7 \times 10^{-8}$); 409 (48%) of which were associated with DEGs in Cluster 3 (2.7 fold-enrichment, $p < 1 \times 10^{-6}$).

A baseline blood transcriptome profile can be used to identify TS patients with 'good' growth and metabolic response to rhGH. In addition genetic variants known to associate with response to rhGH were linked to levels of gene expression in this group. Integrated transcriptomic and genomic analysis represents a novel approach to the personalisation of rhGH treatment for TS.

FC12.5

Integrated analysis of baseline blood transcriptome and genome identifies clusters of Turner syndrome patients with different responses to recombinant human growth hormone

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Responsiveness to recombinant human growth hormone (rhGH) treatment in Turner syndrome (TS) is highly variable. Previous research has characterised genetic variants associated with rhGH response but these only have a minor impact. The relationship of these genetic variants to the blood transcriptome is unknown. The aim of this analysis was to relate unsupervised baseline blood transcriptome and genetic data from TS patients to their phenotype, karyotype and responsiveness to rhGH.

Data on 91 TS patients from the PREDICT study were analysed. Patients were assessed for change in clinical biomarkers over the first month of treatment including IGF-I, IGFBP-3, tri-glyceride levels and insulin resistance (measured by homeostatic model assessment). Annual change in height was measured for five years after the commencement of rhGH treatment. Pharmacogenomic analysis was performed using 11 single nucleotide polymorphisms (SNPs) previously associated with rhGH response, along with baseline transcriptome (mRNA) from blood. Unsupervised analysis of the transcriptome was conducted using Principal Component Analysis (PCA). Patients were clustered by expression profiles using similarity network fusion (SNF). Genetic and transcriptomic data were linked by defining expression quantitative trait loci (eQTL).

Using 9963 transcriptomic probes, 91 TS patients were clustered by PCA. Three patient clusters (Clusters 1, 2 and 3; n=31, 32, 28) were identified using SNF. A profile of 7851 differential expressed genes (DEGs) defined these patient clusters ($0.05 > q > 1.8 \times 10^{-20}$, q =false-discovery modified p-value). For the first year of rhGH treatment, Cluster 3 displayed greater height velocity (HV1) in comparison to other clusters (Clusters 1, 2 and 3; mean HV1 (cm/yr \pm standard deviation[SD])= 7.1 ± 0.9 , 7.2 ± 1.2 , 8.6 ± 1.6 ; $p < 0.009$), as well as a greater decrease in fasting triglyceride over the first

FC12.6

An integrated systems biology analysis of the genome, epigenome and transcriptome identifies a distinct pattern of hypermethylation associated with low childhood growth

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Background: Current data from genome wide association studies (GWAS) explains 24.6% of the variation in adult height from 3290 single nucleotide polymorphisms (SNPs)¹. Data on the genetic control of growth velocity during childhood is more limited and no previous studies have linked childhood growth to changes in the transcriptome (gene expression) or epigenome (DNA methylation). Here we present a systems biology approach to understand mid-childhood growth velocity using genome wide SNP, transcriptome and epigenome analysis.

Study Design: Height velocity (HV) between ages-7 and 9-years was modelled using a mixed-effects model including gender, age, height at start of analysis and pubertal stage in 6487 normal children from the Avon Longitudinal Study of Parents and Children. Blood transcriptome was available in 947 children age-9 and blood epigenome from 980 children age-7. Differentially methylated regions (DMRs), genomic regions that contain multiple methylation sites (CpGs), were defined using the R package ChAMP. A hyper-network approach was used to integrate differentially expressed genes and methylated CpGs to assess functional association between omic data layers. A GWAS was conducted ($n=4781$) to identify SNPs correlated with HV as a continuous variable. Expression quantitative trait loci (eQTLs) were identified linking GWAS findings to levels of gene expression at age-9.

Results: Height velocity between 7 and 9 years was associated with multi-omic patterns distinguishing children with low (LHV) and high HV (HHV). A greater number of transcriptomic differences (p -value range, 6.9×10^{-5} to $< 1.0 \times 10^{-3}$) were identified in LHV children than HHV (34 LHV vs 23 HHV). This was also apparent in the epigenome, where there was a greater impact with a 7-fold larger number of identified CpGs with differences in methylation (1618 LHV vs 140 HHV, p -range 3.0×10^{-7} to $< 1.0 \times 10^{-3}$).

A highly significant DMR was identified in the LHV: in HOXA5 (corrected- $p<5\times 10^{-3}$), a homeobox regulator involved in morphogenesis. GWAS identified 1264 significant SNPs (p-range 8.4×10^{-8} to $<1\times 10^{-4}$); 485 eQTLs were detected across 253 unique genes. GWAS results included 116 significant SNPs associated with the growth hormone receptor (corrected- $p=1.1\times 10^{-3}$), and 52 SNPs associated with MSRA (corrected- $p=5.8\times 10^{-5}$), a gene implicated in biological aging and insulin resistance – both of which also had eQTLs.

Conclusions: We have demonstrated that in normal children (1) a distinct hypermethylation pattern is associated with low, but not high, height velocity and (2) HV-related polymorphisms in growth and metabolic genes are linked to levels of gene expression across the genome.

¹ Yengo, L., et al. Hum.Mol.Gen 2018;27(20):3641-3649.

but different modifications in the activation motif. Three peptides reduced ACTH-stimulated MC2R activity indicated by a reduced cAMP response *in vitro*. Cells pre-incubated with the peptidomimetic LNP009 showed the most efficient blockade of the MC2R and a reduced expression of the steroidogenic enzymes CYP21A2, CYP11B1 and HSD3B2, while having no antagonistic effect up to 1 μM at MC3, MC4, or MC5 receptors. Further peptides are currently developed and tested in our cell systems which are chemically optimized by incorporation of synthetic non-natural amino acid components.

In conclusion we present three peptide antagonists blocking the MC2R pathway, which could be a promising treatment approach for CAH patients. The ultimate goal is to offer patients a novel treatment strategy lacking the side effects of the currently used ACTH-suppressing corticoid therapy.

Adrenals and HP Axis

FC13.1

Peptide MC2R antagonists as a new potential therapeutic approach for congenital adrenal hyperplasia

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Current hormone substitution therapy of patients with congenital adrenal hyperplasia (CAH) is suboptimal and cannot mimic physiological daily rhythms of hormone secretion. As supra-physiological corticoid doses are necessary to avoid adrenal androgen excess, patients show substantially increased comorbidities such as hyperglycemia, arterial hypertension, reduced growth and osteoporosis. Moreover plasma ACTH is often inadequately suppressed, resulting in undesired excess adrenal androgen production causing accelerated bone maturation, virilisation and early puberty. This therapeutic situation is unsatisfactory and demands innovative treatment options. At present there is no effective medical treatment that would directly block the action of ACTH at the highly selective melanocortin 2 receptor (MC2R). Such a therapy would be of great clinical value allowing a strategy of blocking ACTH action and replacing with physiological hydrocortisone doses.

The aim of our study is to inhibit ACTH binding and signal transduction by blocking the MC2R stimulation with potent and selective antagonist peptides. Different newly synthesized peptides were investigated for antagonist activity on MC2R in stably transfected human embryonic kidney cells (HEK293) and in the human adrenal tumor cell line NCI-295RA. These peptides show a high structure homology to ACTH as they have the same binding motif

FC13.2

Sexual dimorphism in cortisol production and metabolism throughout pubertal development: a longitudinal study

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Background: Sex differences in disease susceptibility might be explained by a sexual dimorphism in hypothalamic-pituitary-adrenal axis activity, which has been postulated to emerge during puberty. The aim of this study is to assess the contribution of pubertal development to sexual dimorphism in cortisol production and metabolism.

Methods: Participants, born between 1995 and 1996, were enrolled from the population-based Netherlands Twin Register. At the ages of 9, 12 and 17 years Tanner pubertal stage was assessed, and early-morning urine samples were collected. Cortisol metabolites were measured with GC-MS/MS, and ratios were calculated, representing the activities of various enzymes involved in the metabolism of cortisol. Using the Markov Model, cortisol production and metabolism parameters were compared between sexes for pre-pubertal (Tanner stage 1), early-pubertal (Tanner stage 2-3) and late-pubertal (Tanner stage 4-5) stages. In addition, changes in cortisol parameters between pubertal stages were assessed for both sexes.

Results: 218 participants were included (94 monozygotic and 124 dizygotic twins of which 38 opposite-sex twins) and 542 samples were analyzed; 213, 167 and 162 at 9, 12 and 17y, respectively. In both sexes cortisol production rate decreased with pubertal progression, albeit with few differences between sexes (females 0.581-0.577; p=0.91 and 0.577-0.448; p<0.001, males 0.571-0.512; p=0.04 and 0.512-0.487; p=0.58, from pre- till early- and early-till late-pubertal stage, respectively). A-ring reductase activity was similar in both sexes at pre- and early-pubertal stage, and decreased significantly in females in late pubertal development. A-ring reductase activity was significantly discordant between sexes at late-pubertal stage (being lower in females, 5 α -reductase activity: THF/cortisol 5.50 vs 8.56; p<0.001, 5 β -reductase activity: THF/cortisol 26.10 vs 30.47; p=0.046), while cortisone metabolism was not (THE/cortisone 9.8 vs 10.7; p=0.23). In females, as compared to males, 11 β -HSD type 2 activity was significantly lower (0.77 vs 0.92; p=0.027) at early-pubertal stage, and overall 11 β -HSD activity ((THF+allo-THF)/THE) was lower at both early- and late-pubertal stage (0.55 vs 0.64; p=0.04 and 0.67 vs 0.79; p=0.008). Cytochrome P450 3A4 (6-OH cortisol/cortisol) activity did not differ significantly between sexes.

Conclusion: We found dynamic changes in cortisol production and cortisol metabolism activity during pubertal development. A sexual dimorphism in the activities of A-ring reductases and 11 β -HSDs became manifest during pubertal development, with lower activities in females. Our findings suggest that the sexual dimorphism in cortisol production and metabolism might be attributed by gonadal steroids.

FC13.3

YAP1-HIPPO pathway as a novel prognostic marker and therapeutic target for pediatric patients with adrenocortical tumors (ACT)

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Background: There is no effective adjuvant therapy for patients with advanced ACT. YAP1, a HIPPO pathway effector, interacts with Wnt/beta-catenin pathway and plays a crucial role in the maintenance of postnatal adrenal cortex and regulates cell proliferation and apoptosis in several tissues. We recently showed that overexpression of YAP1 associates with worse prognosis in our cohort of pediatric ACT (pACT).

Aim: To analyze the association of YAP1 expression in ACT with prognosis in additional cohorts of ACT and the effects of YAP1 inhibition on adrenocortical tumorigenesis.

Methods: YAP1 mRNA expression in ACT was analyzed in silico using public available data both in pACT (GSE76019; n=34) and adult ACT (TCGA; ACC=76). In vitro, H295 ACT cells were treated with Verteporfin (VP; 10uM), a FDA-approved drug that inhibits YAP1/TEAD complex. Transient YAP1 knockdown was also performed. The mRNA expression of the HIPPO pathway genes (*LATS2*, *STK3*, *STK4*), its target (*CTGF*), *CTNNB1* (beta-catenin) and cell cycle progression markers (*CCND1*, *CKD2* and

CCNE1) was evaluated by qPCR. The protein expression of YAP1, phospho(p) YAP1 (Ser127), Beta-catenin, Cyclin D1 and mesenchymal markers (Vimentin, N-cadherin and Snail) was analyzed by Western blot. Cell proliferation (MTS), cell invasion (Matrigel coated transwell), cell cycle (flow cytometry) and tumorigenic potential (anchorage-independent growth/soft agar colony formation) were also assessed.

Results: Bioinformatic analysis showed that higher *YAP1* mRNA expression was associated with lower disease free survival (DFS) in pediatric patients (p=0.001) and also with lower DFS (p=0.0004) and total survival in adults (p=0.009). In vitro, VP reduced cell proliferation (48h=-53% and 72h=-67%; p<0.05), invasion (-85%; p<0.05) and abolished anchorage-independent growth. VP reduced mRNA expression of *CTNNB1* (p<0.05), cell cycle genes (*CCND1*, *CDK2* and *CCNE1*; p<0.005) and *CTGF* (p<0.05) while increased mRNA expression of the HIPPO pathway genes (*LATS2*, *STK3* and *STK4*; p<0.05). VP reduced protein levels of YAP1 and pYAP1 (-88% and -94%; p<0.0005), B-catenin (-50%, p<0.001) and the mesenchymal markers Vimentin (-36%, p<0.01), N-cadherin (-66%, p<0.001) and Snail (-53%, p<0.05). YAP1 knockdown reduced cell tumorigenic potential, the expression of mesenchymal markers (Vimentin: -42%, p<0.05; N-cad: -68%, p<0.001) and Cyclin D1 (-43%, p<0.005), while induced G0/G1 cell cycle arrest.

Conclusions: *YAP1* overexpression is a marker of unfavorable prognosis in pediatric and adult ACT patients. *YAP1* signaling inhibition has antitumor effects in ACT cells, as shown by decreased cell proliferation, Beta-catenin downregulation, reduction of cell invasion, loss of anchorage-independent growth and reversion of epithelial-mesenchymal transition. *YAP1* inhibition by Verteporfin may emerge as a potential adjuvant therapy for patients with ACT.

FC13.4

Biphasic glucocorticoid rhythm in one month old infants: reflection of a developing HPA-axis?

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Background: The hypothalamus-pituitary-adrenal (HPA) axis displays a diurnal rhythm, peaking in the morning and with a nadir at night. However, not much is known about the development of the HPA-axis, although strikingly some evidence suggests that a

rhythm with a peak in the afternoon is already present antenatally. We aimed to describe HPA-axis activity at age 1 month as well as study possible influencing factors.

Methods: Fifty-five mother-infant pairs collected breastmilk and infant saliva samples before every feeding moment for 24 hours one month postpartum. Glucocorticoid (GC, i.e., cortisol and cortisone) concentrations were measured with LC-MS/MS, and data were transformed in the rhythm parameters area-under-the-curve (AUC) increase (i) and ground (g), maximum and time of maximum. Analyses were performed with SPSS and Sigma-plot. Maternal psychopathology (increased Hospital Anxiety and Depression Scale and/or consultation at the Psychiatric-Obstetric-Pediatric clinic), season at sampling, sex and breastmilk GC rhythm parameters were assessed for possible associations.

Results: A significant GC rhythm was detected, which was found to be biphasic with peaks at $6:53 \pm 1:01$ (mean \pm SEM) and $18:36 \pm 1:49$ for cortisol, and at $8:50 \pm 1:11$ and $19:57 \pm 1:13$ for cortisone. Maternal psychopathology, season at sampling and sex did not influence the infants' GC rhythm. Breastmilk maximum cortisol levels were positively associated with cortisol AUC_i and maximum levels in the infant. Higher breastmilk cortisone AUC_i, AUC_g and maximum concentrations were associated with an earlier time of maximum in the infant. Additionally, breastmilk and infant GC concentrations were associated between 6:00–9:00, but not during other time intervals.

Conclusion: A biphasic GC rhythm is present in 1-month-old infants at a group level, with peaks in both the morning and the evening, which might be a part of the developmental process towards an adult-type GC rhythm. Maternal psychopathology, season at sampling and sex were not associated with neonatal GC rhythmicity. However, although results were not consistent between cortisol and cortisone outcomes, breastmilk GC parameters might influence the infants' GC rhythm, since a more variable breastmilk GC rhythm was associated with an earlier time of maximum in infants. This could be due to either a causal effect of breastmilk GCs, or because of increased mother-infant synchrony. These findings offer a promising insight into the development of an HPA-axis rhythm, especially with regard to the role of breastmilk, and future research should further elucidate these results.

FC13.5

SGPL1 deficiency leads to downregulation of key enzymes within the steroidogenic pathway

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Background: SGPL1 deficiency is associated with a pathological accumulation of sphingolipid intermediates and a multi-

systemic condition incorporating primary adrenal insufficiency. Sphingolipid intermediates such as ceramide, sphingosine and sphingosine 1-phosphate are postulated to act as modulators of the steroidogenic pathway, often acting as second messengers altering downstream expression of steroid responsive transcriptional elements. Ceramide and sphingosine are largely inhibitors of steroidogenesis with sphingosine acting as an endogenous antagonist to steroidogenic factor 1 (SF-1) maintaining it in an inactive conformation whilst acute activation of S1P signalling in H295R cells leads to increased transcription of STAR and hormone sensitive lipase (HSL) culminating in an increase in cortisol production. Pathological accumulation of these sphingolipid intermediates as seen in SGPL1 deficiency may therefore have negative implications for the steroidogenic cascade.

Objective and Hypotheses: Investigation of the impact of SGPL1 deficiency on steroidogenesis using patient derived human dermal fibroblasts and RNA-seq interrogation of the differential expression of steroidogenic genes in an SGPL1-KD human adrenocortical cell line.

Methods: 1. Primary cell cultures of human dermal fibroblasts were established from skin biopsies of two patients with SGPL1 mutations (Patient 1 - p.F545del; Patient 2 - p.S65Rfs*6G) and primary adrenal insufficiency. The steroidogenic capacity of cultured fibroblasts was explored using a precursor substrate, progesterone, as a stimulator of cortisol accumulation. Culture media from treated and untreated cells were subjected to cortisol measurement (ELISA). STAR expression was quantified by RT-qPCR. 2. Lentiviral shRNA mediated KD of SGPL1 in a human adrenocortical cell line (H295R) with subsequent RNA-seq interrogation.

Results: Wild-type (control) dermal fibroblasts showed a significant cortisol response after progesterone stimulation ($p < 0.001$). In comparison Patient 1 fibroblasts were significantly less responsive to stimulation ($p < 0.05$) and Patient 2 cells were unresponsive to stimulation with no cortisol production ($p < 0.001$). Concurrently, mRNA expression of STAR was significantly reduced (5-fold change, $p < 0.001$) in patient 2 fibroblasts compared to control. Differential gene expression data from RNA-seq revealed functional enrichment of genes for the metabolism of steroids (FDR 0.045) and cortisol synthesis and secretion (FDR 0.0496). Further interrogation revealed significant downregulation of steroidogenic genes, with reduced transcript levels of STAR, CYP21A2 and CYP11B1 in the SGPL1-KD H295R.

Conclusion: Our results are in keeping with a prominent role for sphingolipids in modulating the acute phase of steroidogenesis, suggesting that alterations in sphingolipid metabolism due to SGPL1 deficiency negatively impact the expression of genes responsible for steroid hormone biosynthesis.

FC13.6**Insights into the role of cortisol in the formation of the Clock/Bmal1 complex and its interaction with dsDNA, via molecular dynamics simulations**

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Background: The circadian rhythm-generating peripheral Clock/Bmal1 heterodimer complex regulates the circadian activities of many biological systems, including the hypothalamic-pituitary-adrenal (HPA) axis, by trans-activating or trans-repressing downstream target genes.

Objective and Hypotheses: To investigate the potential role of elevated cortisol in Clock/Bmal1 heterodimer complex-generated circadian biorhythms, both during its normal early morning circadian surge and during the stress response.

Methods and Results: We deployed an *in silico* pipeline of structural bioinformatics, thermodynamics and molecular dynamics. Our study showed that at high concentrations, cortisol intercalates into the minor grooves of dsDNA. This widens the adjacent major grooves and allows to the Clock/Bmal1 heterodimer complex more space to dock in and to interact with dsDNA. Then, the high electrical charge of cortisol appears to attract the alpha helices of the Clock/Bmal1 complex, bending it inwards and establishing stronger interactions with the dsDNA. This may result in a stronger and more prolonged signaling of the biological clock when cortisol is elevated.

Conclusions: Our results indicate that the elevated cortisol levels in the early morning circadian surge and during stress facilitate enhanced and prolonged Clock/Bmal1- dsDNA interactions, potentially serving as an ultrashort positive feedback loop between the biological clock and the HPA axis.

GH and IGF1

FC14.1**Inhibition of IGF1R by IGF1R/IR inhibitor OSI906 as a targeted therapy for glioblastoma: *in vitro* & *in vivo* studies**

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Background: CNS tumours are the most frequent solid tumours in children. In pediatric gliomas, IGF1R nuclear localization was significantly associated with both high grade tumours and increased risk of death and contributed to the aggressive phenotype of glioblastoma by increasing motility and metabolism of tumour cells rather than increasing its proliferation. For children chemotherapy after surgical resection is the mainstay of therapy. However, the best regimen needs to be determined.

Aim: To characterize the response of glioblastoma cells to treatment with OSI906 (IGF1R/IR dual inhibitor) alone or in combination with Temozolomide used as a current adjuvant chemotherapy for pediatric patients.

Methods: stably transfected U87Mg glioblastoma cells with 5 times basal expression of wild type mature GFP-IGF1R fusion protein (wt-IGF1R, WtU87) or GFP-IGF1R fusion protein mutated in Lys1025-1100-1120 to avoid IGF1R nuclear translocation (m-IGF1R, MutU87) were used for *in vitro* and *in vivo* assays. Proliferation assays were carried out for 3 days using complete media (10%FBS), or in the presence of IGF1R/IR inhibitor OSI906 (0.5uM), Temozolomide (TMZ, 40 or 100uM) or the combination of both treatments. Male nude mice were injected for *in vivo* experiments (1.5×10^6 cells/flank/mice). OSI906 (50mg/kg) and TMZ (400mg/kg) were given by gavage once daily or as a single dose respectively. Treatments were started when tumours reached 150 mm³.

Results: After 24 h of culture, MutU87 cells showed decreased proliferation when treated with TMZ40 and OSI906; OSI906 had an additive effect when combined with TMZ40 compared to control condition. However, cells resumed proliferation after 3 days in culture. On the contrary, treatment with TMZ100 had a strong inhibitory effect, that was not increased by the combination with OSI906. WtU87 treated with TMZ40 or 100 also resumed proliferation after 24 h treatment, although the total number of cells was decreased compared to control. OSI906 was able to abolish proliferation of WtU87 cells when used alone or in combination with TMZ 40 or 100, having the latter the strongest effect. *In vivo* studies showed similar trends.

Conclusion: The capacity of the IGF1R to translocate to the nucleus, renders glioblastoma cells sensitive to the IGF1R targeted therapy alone or in combination with TMZ, *in vitro* and *in vivo*. These results suggest that the use of IGF1R inhibitors in pediatric patients showing nuclear localization for this receptor, could be useful to reduce TMZ doses and/or avoid radiotherapy in children.

FC14.2

Pubertal Onset in 1572 girls with Short, Normal and Tall Stature: Associations to height, serum IGF-I and PAPP-A2 genotypes

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Background: Sexual maturation is closely linked to growth, suggesting common pathways between the reproductive development and the growth hormone/insulin-like growth factor-I (GH/IGF-I) axis. IGF-I bioavailability is regulated by Pregnancy associated plasma protein-A (PAPP-A), Pregnancy associated plasma protein-A2 (PAPP-A2) and Stanniocalcin 2 (STC2). A large genome-wide association study (GWAS) identified PAPP-A, PAPP-A2 and STC2 to represent loci strongly associated with adult height.

Aims: The aim of this study was to explore the association between height, serum IGF-I, genotypes of PAPP-A, PAPP-A2, STC2 and pubertal timing in a large cohort of healthy girls and in a cohort of girls diagnosed with short and tall stature.

Method: 1572 girls were recruited from two population-based cohorts of healthy Danish children (n=1382), a cohort of patients with short stature (n=124) and tall stature (n=67). Anthropometrics, assessment of pubertal stages and IGF-I SDS were included. The girls were genotyped for *PAPPA* (rs751543), *PAPPA2* (rs1325598) and *STC2* (rs889014). A Mendelian randomization approach was used to assess the association between height and puberty.

Results: A dose-dependent association between the minor allele of *PAPPA2* and height was observed. Girls homozygous for the minor allele (TT) were -0.27 [-0.47; -0.08] SDS shorter and CT heterozygotic girls were -0.09 [-0.25; 0.06] SDS shorter compared to CC major allele carriers ($p=0.03$). The association remained significant after correcting for IGF-I. We found no significant association between *PAPPA* and *STC2* and height.

Age of pubertal onset was significantly later in girls with short stature (11.19 [10.86; 11.52] years) and earlier in the tall girls (9.25 [8.82; 9.69] years) compared to girls with normal stature 9.96 [9.85; 10.07] years ($p<0.01$). Age at menarche was significantly later in girls with short stature 13.96 [13.55; 14.37] years compared

to girls with normal stature 13.09 [13.00; 13.18] years ($p<0.01$). Adjusting for BMI did not essentially change the estimates. The genotypes were not associated with pubertal onset and menarche.

Girls within the highest IGF-I SDS quintile (Q5) had earlier pubertal onset (B2) and age at menarche compared to girls in Q1-Q4 ($p<0.01$).

Conclusion: We found a significant association between PAPP-A2 genotype and height in this large well-characterized cohort of girls. Height and IGF-I SDS, but not PAPP-A, PAPP-A2 and STC2 genotypes, were negatively associated with age at pubertal onset and menarche.

FC14.3

Papp-a2 deficiency induces sex-specific changes in hydroxyapatite-(CaOH) crystallinity and the effects of IGF-1 on bone composition in adult mice

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Deficiency of pregnancy-associated plasma protein-A2 (PAPP-A2), a regulator of IGF-1 availability, causes postnatal growth failure in humans and mice, at least in part through dysregulation of bone size and density. The present study aimed to determine the effects of *Pappa2* gene deletion and the response to recombinant murine IGF-1 (rmIGF-1) on femur microstructure and composition. Hydroxyapatite-related crystallography and ionic substitutions were analyzed by X-ray powder diffraction (XRD) and Attenuated Total Reflection-Fourier Transform Infra-Red (ATR-FTIR) spectroscopy. Gene expression of members of the IGF-1 system was measured in tibia. Male and female *Pappa2* knock-out (ko/ko) mice had reduced body length in the peripubertal and adult periods. In adulthood, the femurs and tibias were shorter in *Pappa2*^{ko/ko} mice of both sexes and weighed relatively less in *Pappa2*^{ko/ko} males compared to same-sex controls. *Pappa2*^{ko/ko} male bone had: 1) Altered hydroxyapatite-(CaOH)-related crystallinity and crystallite size; 2) Increased content of phosphates (PO⁴³⁻) and carbonates (CO³²⁻; C-O); 3) Increased expression of *Igfbp3*, *Igfbp5* and *Igfals*; and 4) Dynamic increases in phosphate (PO⁴³⁻) and carbonate (C-O) content, and decreases in amide (OH⁻; C=O) content after a single administration of rmIGF-1 (0.3 mg/kg). *Pappa2*^{ko/ko} female bone had: 1) No change in crystallinity or ionic content; 2) Reduced expression of *Igfbp3* and *Igfbp5*; and 3) Increased content of phosphates (PO⁴³⁻), carbonates (CO³²⁻; C-O) and amides (OH⁻) and

4) Higher expression of *Igfbp3* and *Igfbp5* after rmIGF-1 administration. In summary, acute treatment with recombinant IGF-1 modifies hydroxyapatite-related ionic substitutions and local IGF-1 system in the bones of mice with *Pappa2* deficiency. These effects depend on sex and provide important insights into IGF-1 efficacy as potential therapy for growth failure.

FC14.4

Once-Weekly TransCon hGH vs. Daily hGH in Pediatric Growth Hormone Deficiency: The Phase 3 heiGHT Trial

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Background: TransCon hGH is a sustained-release prodrug in development as a long-acting GH for children with growth hormone deficiency (GHD). TransCon hGH consists of a parent drug, growth hormone (hGH; somatropin), that is transiently bound to a carrier via a TransCon linker. The carrier extends hGH circulation time in the body and fully active hGH is released over one week at physiologic pH and temperature. Unlike other molecules in development, TransCon hGH is designed to deliver unmodified hGH with the same mode-of-action and distribution as daily hGH replacement therapy but with convenient once-weekly dosing.

The aim of the pivotal phase 3 global heiGHT trial was to investigate the safety, tolerability, and efficacy of weekly TransCon hGH versus daily hGH over 52 weeks in treatment-naïve prepubertal children with GHD.

Methods: Subjects (N = 161) were randomized 2:1 to receive once-weekly TransCon hGH 0.24 mg hGH/kg/wk or dose-equivalent once-daily Genotropin. The primary endpoint was annualized height velocity (AHV) at 52 weeks, and the trial was powered to demonstrate non-inferiority.

Results: Baseline demographics were similar between the two groups. AHV at 52 weeks was 11.2 cm/y for the TransCon hGH group vs. 10.3 cm/y for the daily Genotropin group (P = 0.0088), with TransCon hGH demonstrating both non-inferiority and superiority over Genotropin. IGF-1 standard deviation score (SDS) was generally within the normal range following treatment for each group. Over 52 weeks, the bone age/chronological age ratio (BA/CA) increased in both groups: by 0.06 to 0.75 for TransCon hGH, and by 0.05 to 0.76 for Genotropin. Bone age advancement was similar in both groups: by 0.17 to 2.33 years for TransCon

hGH, and by 0.17 to 2.13 years for Genotropin. TransCon hGH was generally safe and well-tolerated, with adverse events consistent with the type and frequency observed with daily Genotropin. No neutralizing antibodies were detected, and the low level of low-titer non-neutralizing antibodies was similar between groups. Additional analyses will include efficacy by subgroups (e.g., age, gender, baseline stimulated GH strata, GHD etiology and extent), and glycemic and hormonal parameters over time.

Conclusions: In the phase 3 heiGHT trial, treatment with TransCon hGH achieved the primary objective of non-inferiority in AHV at 52 weeks, and further showed superiority over Genotropin. These results suggest that TransCon hGH may offer a convenient alternative, once-weekly hGH therapy for children with GHD, while maintaining a similar safety profile to daily hGH.

FC14.5

Once-weekly somapacitan vs daily growth hormone (Norditropin[®]) in childhood growth hormone deficiency: One-year results from a randomised phase 2 trial

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Daily injections are required for human growth hormone (GH) replacement therapy. Somapacitan is a long-acting GH derivative being developed for once-weekly dosing in adults and children using a proven protraction method, currently successfully in use to extend the half-life of insulin and glucagon-like peptide 1.

To evaluate the efficacy and safety of three different once-weekly somapacitan doses compared with Norditropin[®], a daily GH, over 52 weeks in GH-treatment-naïve prepubertal children with GHD.

In this multicentre, open-label, randomised, controlled, double-blinded (with respect to dose), phase 2 study (ClinicalTrials.gov: NCT02616562), participants were randomised to somapacitan (n=45) or Norditropin[®] (n=14). Patients received 0.04 (n=16), 0.08 (n=15) or 0.16 (n=14) mg/kg/week subcutaneous somapacitan once weekly, or subcutaneous Norditropin[®] 0.034 mg/kg/day; n=14). Patients (n=56, 94.9%) completed 52 weeks of treatment: somapacitan 0.04 (n=14), 0.08 (n=15) and 0.16 (n=14) mg/kg/week, and Norditropin[®] 0.034 mg/kg/day (n=13).

At 52 weeks, mean (SD) annualised height velocity (HV, cm/year) for the three somapacitan doses was 7.8 (1.8), 9.7 (1.8) and 11.5 (2.6), respectively. HV for the 0.16 mg/kg/week dose was statistically significantly higher than for Norditropin[®] (10.0 [2.2])*. HV for the 0.08 mg/kg/week dose did not differ significantly from HV with Norditropin[®]. Mean (SD) change from baseline in HV

standard deviation score (SDS) was 4.72 (2.79), 6.14 (3.36) and 8.60 (3.15) for the three somapacitan doses, respectively, and not significantly different from Norditropin^{*} (7.41 [4.08]) for somapacitan 0.08 or 0.16 mg/kg/week. Derived mean (SD) insulin-like growth factor-I SDS for somapacitan 0.04, 0.08, and 0.16 mg/kg/week was -1.62 (0.86), -1.08 (0.81) and 0.41 (1.05), respectively, compared with -0.40 (1.50) observed for Norditropin^{*}. Change in bone age appeared similar among all treatment groups. Adverse events (AEs) were generally mild to moderate in severity and most were considered unrelated to treatment. The rate of AEs for the highest dose of somapacitan (0.16 mg/kg/week) was the same as for Norditropin^{*}. Five subjects had one single low-titre measurement of non-neutralising anti-somapacitan antibodies.

In children with GHD, the efficacy, safety and tolerability of once-weekly somapacitan were similar to those of daily GH, with the 0.16 mg/kg/week dose providing the closest overall efficacy match. These results provide support for the initiation of a phase 3 trial of somapacitan in children with GHD.

* Post-hoc defined analysis excluded one subject in the Norditropin^{*} group, who prematurely discontinued treatment.

FC14.6

Effects of 8 years of growth hormone treatment on cognition in children with Prader-Willi syndrome

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Context: Children with Prader-Willi syndrome (PWS) generally have mild to moderate cognitive impairment with an IQ between 60 and 70. Growth hormone (GH) treatment is a registered treatment for children with PWS and has been associated with cognitive benefits, attributed to the effects of GH and insulin-like growth factor on brain growth and development. Short-term data suggest positive effects of GH treatment on cognitive functioning in children with PWS. There are, however, no long-term studies about the effects of GH on cognitive functioning.

Objective: To investigate the long-term effects of GH on cognitive functioning in children with PWS. Secondly, to investigate whether starting GH before the age of 2 years, results in higher cognitive functioning after 8 years of GH.

Design: Prospective cohort study during 8 years of GH.

Setting: Dutch PWS Reference Center

Intervention: All children were treated with GH 1 mg/m²/day (\approx 0.035 mg/kg/day).

Main outcome Measures: Cognitive functioning assessed by the Wechsler Intelligence Scale for Children-Revised (WISC-R). Vocabulary, Similarities and Block Design subtests were used and expressed as standard deviation scores. Total IQ (TIQ) was estimated.

Results: Forty-three children with PWS (29 girls), started GH at a median (IQR) age of 8.1 (6.6; 11.5) years. Estimated mean Block Design SDS increased from -2.2 at baseline to -1.8 after 8 years of GH ($p=0.18$), showing that visuospatial skills tended to

improve compared to healthy controls. Estimated mean Similarities SDS increased from -1.5 to -1.3 ($p=0.66$) and Vocabulary SDS remained similar, being -1.9 SDS at baseline and after 8 years ($p=0.85$), demonstrating that children with PWS develop abstract verbal reasoning and vocabulary at the same pace as healthy references. Mean estimated TIQ improved from 66 points at baseline to 69 points after 8 years of GH ($p=0.57$).

Another group of 20 children started GH before the age of 2 and had a significantly higher Vocabulary SDS and estimated TIQ after 8 years of GH ($p<0.01$ and $p=0.04$, resp.) than the children who participated in the current study. Scores on the Block Design and Similarities subtest were similar between the two groups ($p=0.53$ and $p=0.19$, resp.).

Conclusions: Our results demonstrate that cognitive skills in children with PWS are maintained during 8 years of GH, indicating that GH-treated PWS children develop at the same pace as healthy references. We also conclude that starting GH treatment before the age of 2 years might lead to higher cognitive functioning on the long-term.

Late Breaking Abstracts

FC15.1

DLG2 mutations in patients with delayed or absent puberty

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NMDA (N-Methyl-D-aspartic acid) receptors have been shown to control the timing of sexual maturation in laboratory animals. Therefore, variants in genes impacting NMDA receptor signaling might be predicted to affect human puberty. We studied an extended family with extremely delayed puberty (menarche at 16.5 - 18 years for female family members and pubertal onset at 16 years for male family members). Exome sequencing revealed a rare missense variant (F900V) in *DLG2*, which co-segregated precisely with the delayed puberty phenotype in the 5 affected members of the 11-member family. Interestingly, recent genome-wide association studies (GWAS) have implicated *DLG2* in the normal timing of human puberty in males and females. *DLG2* encodes PSD-93, an anchoring protein of NMDA receptors. The functional effects of PSD-93 F900V were studied *in vitro*. First, we assessed the effect of F900V on the interaction between PSD-93 and Fyn, a known binding partner of PSD-93 that phosphorylates NMDA receptors to increase signaling. Co-immunoprecipitation showed that the F900V variant impaired the interaction between PSD-93 and

Fyn ($P=0.005$). Second, the impact of F900V on the expression of *Gnrh1* was studied in the hypothalamic cell line, GT1-7. Compared to wild-type *Dlg2*/PSD-93, F900V decreased expression of *Gnrh1* both in mRNA expression by real time-PCR ($P=0.003$) and GnRH peptide/total protein ratio by ELISA ($P=0.008$). We next looked for *DLG2* sequence variants in a large cohort of 1,327 individuals with hypogonadotropic hypogonadism (HH) and identified missense variants in *DLG2* that also significantly diminished *Gnrh1* mRNA expression *in vitro* in 3 unrelated families with HH: two siblings with normosmic HH, 2 siblings with Kallmann syndrome, and a single subject with Kallmann syndrome. However, incomplete penetrance indicated that the *DLG2* variants alone were not sufficient to cause HH, suggesting a digenic or oligogenic inheritance. We observed mRNA expression of *Dlg2* in the rat preoptic area and protein expression in mouse hypothalamus which varied with age. However, the temporal pattern of expression did not match the temporal pattern of reproductive maturation suggesting that, although *Dlg2*/PSD-93 may be important for normal puberty, rising expression may not be a trigger for pubertal onset.

In conclusion, variants in *DLG2*/PSD-93, an anchoring protein of NMDA receptors, were found in an extended family with extremely delayed puberty and in subjects with HH. *In vitro* studies indicated that the variants affect GnRH expression. The findings provide evidence that abnormalities in NMDA receptor signaling are involved in the pathogenesis of human pubertal disorders.

Methods: We performed exome sequencing in one adolescent boy with non-autoimmune diabetes and his parents. He carried a heterozygous *de novo* *HDAC4* variant (p.His227Arg) with predicted, deleterious protein function. We additionally sequenced a cohort of 94 individuals with paediatric-onset, non-immune diabetes, and lack of mutations in genes up-to-date associated with monogenic diabetes. In mouse pancreatic β -cell lines (Min6 and SJ cells), we performed insulin secretion assay and quantitative RT-PCR to measure the β -cell function transfected with the detected *HDAC4* variants and wildtype. We carried out immunostaining, Western blot and immunoprecipitation to investigate rare *HDAC4* variants from our cohort whether one key process, the cellular translocation and acetylation of Forkhead box protein O1 (FoxO1) in pancreatic β -cells specifically was influenced.

Results: We discovered three *HDAC4* mutations (p.His227Arg, p.Asp234Asn, and p.Glu374Lys) in unrelated individuals that had non-autoimmune diabetes with various degrees of β -cell loss. In mouse pancreatic β -cell lines, we found that these three *HDAC4* mutations decrease insulin secretion, down-regulate β -cell-specific transcriptional factors, all compared to wild-type *HDAC4*. Finally, overexpression of all pathogenic *HDAC4* mutations cause nuclear exclusion of acetylated FoxO1 in β -cells.

Conclusion: Mutations in *HDAC4* disrupt the deacetylation of FoxO1 and thus lead to its nuclear exclusion. Subsequently *in-vitro* β -cell function was decreased and cellular mechanisms identified *in-vitro* might cause diabetes in individuals carrying *HDAC4* mutations.

FC15.2

HDAC4 mutations cause diabetes and induce β -cell FoxO1 nuclear exclusion

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Background: Studying patients with rare Mendelian diabetes has highlighted molecular mechanisms regulating β -cell pathophysiology. Previous, experimental studies have shown that Class IIa histone deacetylases (HDAC4, 5, 7, and 9) modulate mammalian pancreatic endocrine cell differentiation, function and finally glucose homeostasis.

FC15.3

The P450 side-chain cleavage isozyme cyp11a2 facilitates interrenal and gonadal steroid hormone biosynthesis in developing and adult zebrafish

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Cytochrome P450 side-chain cleavage enzyme, encoded by the *CYP11A1* gene, catalyzes the first and rate-limiting step of steroid hormone biosynthesis. Previous morpholino knockdown studies described the divergent functions of the two *cyp11a* paralogs in zebrafish. *Cyp11a1* has been suggested to be required for early development, whereas *cyp11a2* is a functional equivalent of human *CYP11A1* and is essential for the initiation and maintenance of zebrafish interrenal steroidogenesis. To establish a model system with glucocorticoid and sex steroid deficiency, we developed zebrafish mutant lines by creating deletions in *cyp11a2* gene using CRISPR/Cas9 genomic engineering approach. Homozygous mutant zebrafish larvae showed an upregulation of the hypothalamic-pituitary-interrenal (HPI) axis and interrenal hyperplasia. Furthermore, *Cyp11a2*-deficient zebrafish had a steroid profile with decreased glucocorticoid and 11-Ketotestosterone, the key active androgen in zebrafish. Downregulation of the glucocorticoid-responsive genes *fkbp5* and *pck1* and the androgen-responsive gene *cyp2k22* indicated systemic combined steroid hormone deficiencies. *Cyp11a2* homozygotes only developed into males with feminized secondary

sex characteristics. Adult *cyp11a2* null-allele mutant fish showed lack of natural breeding behavior and reduced sperm concentration, suggesting reproductive impairment in adult fish. Histological characterization of the testes revealed disorganized testicular structure and significantly decreased mature spermatozoa. This finding is further supported by the downregulation of the expression of several pro-male genes in the testes of *cyp11a2* homozygous zebrafish, including *sox9a*, *dmrt1* and *amh*. Moreover, *nanos2* and *piwi1*, markers of spermatogonia, were upregulated while *sympc3* and *odf3b*, markers of spermatids, were downregulated in the testes of *cyp11a2* homozygous mutants. The expression analysis is consistent with the histological results suggesting spermatogonia are the dominant cell type in the testes of *cyp11a2* homozygous mutants. Our work demonstrates the crucial role of Cyp11a2 in interrenal and gonadal steroid hormone biosynthesis in zebrafish larvae and adults. It establishes an *in vivo* model allowing studies of systemic consequences of altered steroid hormone deficiency.

FC15.4

Defects in the GnRH Neuroendocrine Network Affect the Timing of Puberty

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Background: Self-limited delayed puberty (DP) is an extreme variant of normal pubertal timing and it often clusters in families. Although it is highly heritable and is the most common cause of delayed puberty, little is known about the genetic control. GnRH neuronal biology has been implicated as a key element in the pathogenesis of DP. By focusing on genes involved in GnRH neuron development, migration and function we may understand more about the genetic basis of this condition.

Objective: To investigate novel genetic pathways in the pathogenesis of DP via analysis of whole exome sequencing (WES) data from our large cohort with familial self-limited DP, particularly with respect to GnRH neuronal biology.

Method: WES data from our large Finnish cohort consisting of 104 DP families have been analysed with a total of 197 individuals: 104 probands, 58 affected and 35 unaffected family members. Initially, variants were filtered for rare, predicted deleterious variants that segregated with trait, and were significantly enriched for pathogenic variants in our cohort by burden testing. Additionally, genes involved in GnRH neuronal development and function have been identified by pathway analysis. Sanger sequencing was performed to validate the findings and to evaluate the correlation between genotype and phenotype, to see whether the variants segregate well with the DP trait within each pedigree.

Results: We have identified 2 candidate genes of interest. Firstly, *CCDC141*, in which we have identified 5 rare, potentially pathogenic missense variants in 20 individuals from 6 families. Homozygous mutation of *CCDC141* have been reported as causal in cases of hypogonadotropic hypogonadism (HH) and Kallmann

Syndrome, due to impaired GnRH migration. The second candidate is *NOS1AP*, in which an in-frame deletion located in the region that interacts with carboxypeptidase E (CPE) was present in 2 families (7 individuals). Although there is no known link between *NOS1AP* and pubertal timing, abnormalities in CPE have been reported to cause HH by abnormal GnRH secretion or impaired dendritic development. Our preliminary work with this variant in *NOS1AP* show that it has increased interaction with CPE via co-immunoprecipitation experiments when compared to wild type *in vitro*. The pathogenicity of each of variant is under investigation.

Conclusion: The preliminary results suggest a causal role for *CCDC141* and *NOS1AP* in self-limited DP. Heterozygous mutations in *CCDC141* lead to impaired GnRH neuron migration, whilst *NOS1AP* may have a role in GnRH secretion via interaction with CPE.

FC15.5

Effects of *Bifidobacterium animalis* subsp. *lactis* on children with Prader-Willi syndrome: A randomized, double-blind, placebo-controlled, crossover trial

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The gut microbiome has recently emerged as a major contributor to obesity and metabolic disease. Specifically, *Bifidobacterium animalis* subsp. *lactis* (BAL) has shown promise for obesity treatment in human subjects, improving body composition and metabolic health. Moreover, tryptophan metabolism, a crucial regulator of satiety mechanisms and anxiety, is a main target of BAL. Given that clinical manifestations of Prader-Willi syndrome (PWS) include hyperphagia, anxiety, altered body composition, and metabolic dysregulation, we tested whether daily supplementation with BAL could prove beneficial for children with PWS.

To this aim, 28 children with genetic diagnosis of PWS (4.5 to 18 year-old, 17 female, mean \pm SD BMI-SDS 1.57 \pm 1.34) were provided with BAL (daily dose of 10 \times 10 cfu) and placebo for 3 months per treatment phase using a randomized double-blind crossover design, with a 3-month washout period between phases. Anthropometric, biochemical, and psychological data as well as biological samples (feces, blood) were obtained at the beginning and end of each phase. The main outcome variable was body composition (percent adiposity), measured by DXA scan. Hyperphagia was assessed with a specific questionnaire for PWS (HQ-CT) and nutritional analysis with a 4-day food record. Emotional and behavioral problems were assessed with a parental-rated validated questionnaire (CBCL) for children between 8 and 18 years of age (n=20). Placebo and probiotic phases were compared using Wilcoxon signed-rank test (for paired samples). No significant carry-over effects were observed.

Daily consumption of BAL significantly decreased percent of abdominal adiposity compared to placebo period (p<0.05).

Furthermore, treatment with the probiotic improved fasting insulin levels and HOMA-IR ($p<0.05$ for both). Other outcome measures, including BMI-SDS, blood pressure, and lipid profile, did not differ between treatment phases. No effect of BAL supplementation was observed on hyperphagia and caloric intake. The CBCL test revealed no changes in anxiety levels but improvements in social withdrawal scores after probiotic supplementation compared to placebo ($p<0.05$). In summary, our data indicates that supplementation with BAL improves abdominal adiposity, insulin resistance, and could ameliorate some behavioral problems in children with PWS. A follow-up study with a longer treatment period will be warranted to determine whether BAL supplementation could provide a strategy for improving long-term health outcomes in children with PWS.

This trial was registered at clinicaltrials.gov as NCT03548480.

FC15.6

Leptin influences the down-regulation of UCP-1 expression in brown adipose tissue during negative energy balance

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Background: The GH/IGF-I axis is involved in metabolic control and studies suggest that IGF-I deficiency and subsequent changes in IGF-I signaling in brown adipose tissue (BAT) modifies its thermogenic capacity. Food restriction reduces thermogenic capacity in BAT, while leptin stimulates thermogenesis through uncoupling protein 1 (UCP-1) induction. Leptin and IGF-I maintain important crosstalk in different tissues, but whether these two hormones interact to regulate thermogenesis in BAT remains unknown.

Objectives: We compared the effect of chronic central leptin infusion, which reduces food intake resulting in weight loss but with high central and circulating leptin levels, with pair-fed (PF) animals that have reduced bodyweight with normal leptin levels, on the GH/IGF-I axis and the activation of IGF-I-related signaling and metabolism related to BAT thermogenesis.

Methods: Eighteen male Wistar rats were divided into control (C), icv leptin infusion (12 µg/day) for 14 days (L) and pair-fed (PF) groups. The mRNA levels of hypothalamic somatostatin, pituitary GH and BAT UCP-1 and UCP-2 were studied by real-time PCR. Serum GH and IGF-I levels and activation of IGF-I receptor (IGF-IR) in BAT were determined by ELISA, association between suppressor of cytokine signaling 3 (SOCS-3) and IGF-IR by immunoprecipitation and glucose transporter 4 (Glut4) levels in BAT by Western blotting. Hepatic activation of signal transducer and

activator of transcription 5 (STAT5) and phosphorylation of STAT3, Akt and cyclic AMP response element binding protein (CREB) in BAT were analyzed by multiplexed bead immunoassay.

Results: Hypothalamic somatostatin mRNA levels were increased in PF and decreased in L rats. Pituitary GH mRNA levels were reduced in PF rats, as were serum GH and IGF-I concentrations and hepatic STAT5 activation, suggesting that a forced reduction in food intake suppresses the systemic GH/IGF-I axis, while the reduction in food intake as a result of leptin infusion does not. In contrast, in BAT the phosphorylation of STAT3 and the association between SOCS3 and IGF-IR were reduced and phosphorylation of IGF-IR, Akt and CREB increased, as well as Glut4 levels in the L group, suggesting that IGF-I signaling is increased, as well as possibly glucose transport. UCP-1 mRNA levels were reduced in PF rats, with no changes in UCP-2 mRNA levels.

Conclusions: BAT metabolism and thermogenesis are differentially affected by a reduction in food intake depending on the hormonal environment. Our results suggest that the differential response of BAT could be related to an interaction between leptin- and IGF-I-related signaling.

Rapid Free Communications

Diabetes and Insulin Session 1

RFC1.1

Low prevalence of maternal microchimerism in Japanese children with type 1 diabetes

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Background: Vertical transfer of maternal cells to the fetus via the placenta leads to maternal microchimerism (MMC) in children. Previous studies from USA have shown that the prevalence and degree of MMC was significantly higher in patients with type

1 diabetes (T1D) than in their unaffected siblings and control individuals. To date, however, the frequency of MMc in non-Caucasian T1D patients remains to be examined.

Methods: We studied 153 Japanese children diagnosed with T1D, including 122 children positive for diabetes-associated autoantibodies, and their 71 unaffected siblings. We examined the prevalence and degree of MMc in the DNA samples extracted from peripheral blood mononuclear cells by the use of quantitative PCR targeting non-transmitted maternal HLA alleles.

Results: MMc was detected in 18 of 122 children with autoantibody-positive T1D, 8 of 31 children with autoantibody-negative T1D, and 11 of 71 unaffected siblings. The prevalence of MMc was slightly higher in children with autoantibody-negative T1D than that of children with autoantibody-positive T1D and unaffected siblings; however, the difference was not statistically significant ($p = 0.18$ [autoantibody-negative T1D vs. autoantibody-positive T1D], $p = 0.28$ [autoantibody-negative T1D vs. unaffected siblings]). The median [minimum-max] MMc levels, calculated from the MMc cells per 100,000 proband cells, were comparable among these three groups (0.0 [0.0-15.4], 0.0 [0.0-12.6], and 0.0 [0.0-18.2], respectively).

Discussion: The prevalence and degree of MMc did not differ among children with T1D with and without autoantibodies and their unaffected siblings. These findings indicate that MMc plays a negligible role in the development of T1D in Japanese children. Notably, the median MMc levels of our patients with T1D were similar to those of the previously reported healthy Caucasian children. The difference in the MMc frequency between the present and previous studies may reflect the difference in the genetic background between Asian and Caucasian patients. Indeed, MMc has previously linked to the Caucasian-predominant risk HLA allele, DQB1*0302-DRB1*04. As yet, it remains unknown whether MMc is involved in autoimmune β -cell destruction or constitutes a protective response against tissue damage. Further studies are needed to confirm the role of MMc in childhood-onset T1D.

RFC1.2

Gabra5 contributes to sexual dimorphism in POMC neural activity and glucose metabolism

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Objectives: To test whether Gabra5 in POMC neurons regulates energy balance and glucose metabolism in sexually dimorphic fashion.

Methods: POMC-Cre mice received stereotaxic injections of AAV-FLEX-scCas9 and AAV-FLEX-Gabra5-sgRNA-tdTomato into ARH to generate pomic-Gabra5 KO mice. Both male and female mice were fed on regular chow diet or HFD. Food intake, body weight and anal temperature were measured every 4 days. Fat/lean mass were measured by QMR. Glucose tolerance test and insulin tolerance test were done before and after HFD feeding. Glucose clamp was also done after 4 weeks HFD feeding.

Results: Neither on chow diet nor HFD, no significant difference was found in food intake, body weight and anal temperature in males and females compared with their controls. Female

Gabra5-KO mice on HFD showed impaired insulin tolerance. While male Gabra5-KO mice on HFD showed improved insulin tolerance.

Conclusions: Specific deletion of Gabra5 in POMC neuron doesn't relate to energy expenditure neither in males nor females. However, pomic-Gabra5 KO could improve glucose tolerance only in male mice, while female mice showed opposite result. These results provide evidence for sex differences in glucose metabolism.

RFC1.3

The Association Between IGF-1 levels and Nonalcoholic Fatty Liver Disease (NAFLD) in Adolescents with Type 2 Diabetes

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Background: Type 2 diabetes (T2D) is an emerging disease in the pediatric population. The mechanisms responsible for the development of nonalcoholic fatty liver disease (NAFLD) and progression to nonalcoholic steatohepatitis (NASH) in these patients are incompletely understood. Low serum insulin-like growth factor-1 (IGF-1) levels are associated with increased histologic severity of NAFLD. Growing evidence suggests that growth hormone (GH) and IGF-1 may have roles in the development and progression of NAFLD.

Objective: To evaluate the association between serum IGF-1 levels with the percentage of liver fat in T2D youths.

Material and Method: This Cross-sectional study included a total of 70 adolescents, 47 adolescents with T2D and 23 healthy adolescents. The protocol was approved by the local Ethics and Research Committees. The characteristics of the study were explained to all the participants; a complete clinical history, anthropometry and physical examination were performed. To evaluate the average of liver fat, the imaging estimated proton density fat fraction (PDFF) was determined by magnetic resonance (MR). The serum IGF-1 levels were analyzed by chemiluminescent immunometric assay.

Results: Mean age was 14.9 ± 2.2 years, and body mass index (BMI) was 23.6 ± 4.6 kg/m². Considering the average PDFF threshold of 6.5% or higher, we had 31 adolescents with T2D and NAFLD, 16 with T2D without NAFLD and 23 healthy adolescents. Mean serum IGF-1 was lower in subjects with NAFLD, $(207.2 \pm 93.1$ ng/ml vs. 241.9 ± 78.6 ng/ml, $p < 0.05$). We observed an association between the percentage of liver fat and IGF-1 levels ($p=0.012$). After a multivariable analysis, the association was non-significant when we adjusted for BMI, severity of NAFLD, or Tanner score. With the exception of the association between IGF-1 levels and NAFLD which remained significant after adjustment for levels of HbA1c.

Conclusions: In adolescents with T2D, low serum IGF-1 levels are associated with increased of the percentage of liver fat (PDFF). Further investigation is warranted to determine the differential effects of GH and IGF-1 on the development and progression of NAFLD in adolescents with T2D, which could further elucidate pathophysiology and identify therapeutic targets.

RFC1.4

Estimation of Mody Frequency and Prevalent Subtypes in Pediatric Patients by Targeted Ngs

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Though up to fourteen different MODY subtypes have been so far described, there are no studies in the literature which have determined their actual frequency and prevalence in pediatric patients.

Objectives: To identify the underlying molecular basis in a cohort of pediatric patients with a suspected clinical diagnosis of MODY by targeted NGS.

Materials/Methods: Cohort of 60 patient fulfilling MODY clinical criteria (presentation before age 25 years, autosomal dominant inheritance, no obesity, negative autoimmunity and partial beta cell function preservation), and 2 neonatal diabetes patients (26 days and 6 months old, respectively). Molecular analysis by targeted NGS with a custom panel (MonDIAB_V1; 173 genes implicated in glucose homeostasis or associated with dysglycemia, including the 14 known MODY genes). Average coverage >100x, % bases with coverage >20x=>90%; variant prioritization using VarSeqV2.1.0. (Golden Helix).

Results: We identified 33 potentially pathogenic heterozygous variants (bioinformatic predictors: CADD>20; DANN >0.98) in 26/60 (43.3%) patients (mean age: 10 ± 3.7 years; range 1-16 years). Seven patients (26.9%) presented digenic inheritance with 2 relevant variants in two different MODY genes. Regarding the prevalent subtypes, 14/33 (42.4%) were identified in GCK (4 missense,

1 frameshift, and 9 missense variants; 2 of which are novel); 7/33 (21.2%) in HNF1A (1 frameshift and 6 missense variants, 1 non previously described); 4/33 (12.1%) in ABCC8 (1 proximal promoter variant in 2 patients and 2 missense variants, 1 non previously described); 2/33 (6.1%) in BLK (2 novel missense variants); and one missense variants in HNF1b, HNF4A, PDX1, PAX4, KCNJ11, and NEUROD1, respectively, all novel. The seven patients with an apparent digenic inheritance presented the following variants combinations: HN4A + PAX4, GCK + ABCC8, HNF1A + ABCC8 (n=3), and GCK+KCNJ11. The 2 patients with neonatal diabetes presented with a previously described heterozygous pathogenic nonsense mutation in KCNJ11 and a novel missense variant in NKX6-2, respectively.

Conclusions: Targeted NGS analysis identified potentially pathogenic variants in known MODY genes in 43.3% of the examined patients.

Up to 26.9% of the patients with relevant variants in MODY genes (11.7% of the examined cohort) presented an apparent digenic inheritance. This represents a much larger proportion than that initially estimated by traditional screening techniques of candidate genes.

56.7% of the examined patients, did not present relevant variants in the 14 known MODY genes, which suggests the implication of other unknown genes in the etiology of MODY.

RFC1.5

Decreased circulating levels of MOTS-c in individuals with newly diagnosed type 1 diabetes children

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Background and Aims: A novel bioactive peptide, mitochondrial-derived peptide (MOTS-c), has recently attracted interests as a potential prevention or therapeutic option for obesity and type 2 diabetes mellitus in mice. MOTS-c profiles have not yet been reported in type 1 diabetes (T1DM). We aimed to determine circulating MOTS-c levels in T1DM and explore the association between MOTS-c levels and various metabolic parameters.

Methods: In this case-control study, 60 age-, sex- matched children were recruited in the Hubei Province of China in 2015-2017. Thirty (16 females and 14 males) of these individuals were newly diagnosed T1DM children and 30 (15 females and 15 males) were of normal glucose. Subjects were excluded if they used medications such as insulin or metformin. MOTS-c levels in the fasting plasma were assessed using a commercially available enzyme-linked immunosorbent assay (ELISA), clinical data (e.g., serum glucose, insulin, C-peptide, HbA1c, and lipid profile) were recorded, and anthropometric measurements were performed. Finally, we investigated correlations between MOTS-c levels and related variables.

Results: Circulating MOTS-c levels were significantly decreased in newly diagnosed T1DM children compared with those in the normal control group (445.45 ± 21.29 ng/mL vs. 565.41 ± 20.19 ng/mL, $p < 0.001$). In addition, when stratified by sex, the trend of plasma MOTS-c reduction was similar in female and male patients with newly diagnosed T1DM (female 438.44 ± 33.06 ng/mL

vs. 557.85 ± 27.85 ng/mL, $p < 0.05$; male 453.47 ± 26.75 ng/mL vs. 572.98 ± 30.08 ng/mL, $p < 0.05$, respectively). Finally, we observed that MOTS-c levels were negatively correlated with random blood glucose ($r = -0.380$, $p = 0.003$), HbA1c ($r = -0.408$, $p = 0.001$), and triacylglycerol ($r = -0.283$, $p = 0.029$), and positively correlated with HDL-cholesterol ($r = 0.294$, $p = 0.023$) and C-peptide ($r = 0.338$, $p = 0.015$).

Conclusions: Circulating MOTS-c levels were decreased in newly diagnosed T1DM children. Although the role of MOTS-c as a treatment for T1DM will require further investigation, it is possible that a decline in MOTS-c might be a biomarker of T1DM children.

Key words: Mitochondrial-derived peptide, MOTS-c, T1DM, children

RFC1.6

An oral trace element supplementation has a potential beneficial effect on glucose homeostasis in transfused patients with β -thalassemia major complicated with diabetes mellitus

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Background: β -thalassemia major (β -TM) is the most common genetically determined chronic hemolytic anemia. Studies reported that patients with β -thalassemia are zinc deficient due to increased utilization of zinc by oxidative stress, increased urinary zinc excretion and sequestration in the liver. The development of abnormal glucose tolerance in β -TM is associated with alteration in oxidant-antioxidant status. Zinc plays an essential element for insulin synthesis, storage and secretion.

Aim: This study investigated the effect of zinc supplementation on glucose homeostasis in pediatric patients with β -TM complicated with diabetes mellitus (DM) and its relation to clinical and laboratory parameters of these patients.

Methods: Eighty patients with β -TM (aged ≥ 10 years old) were recruited from the regular attendants of the Pediatric Hematology Clinic. Each of the eligible children was randomly assigned by simple randomization to either; Group I which included 40 patients who received oral zinc in a dose of 40 mg daily for 3 months duration or Group II which included 40 patients who received placebo. All patients were subjected to detailed medical history and thorough clinical examination. Laboratory investigations included complete blood count (CBC), hemoglobin analysis, markers of hemolysis (indirect bilirubin and lactate dehydrogenase [LDH]), serum ferritin, fasting blood glucose (FBG), fructosamine, fasting C peptide, urinary albumin excretion (UAE) and serum zinc levels were assessed. All patients were clinically followed-up for 3 months with assessment of biochemical indices for evaluating the

effects and compliance of zinc supplementation and for monitoring signs of any potential adverse effect.

Results: Comparison between baseline clinical and biochemical data among β -TM patients in both groups showed no significant difference. In our study, all the enrolled thalassemia patients had significantly lower zinc levels compared with healthy controls ($p < 0.001$). At 12 weeks, indirect bilirubin, LDH, serum ferritin, FBG, fructosamine and UAE were significantly lower while hemoglobin levels and fasting C peptide were significantly higher after zinc supplementation compared with baseline levels or with placebo group ($p < 0.05$). Baseline serum zinc was negatively correlated to FBG ($r = -0.534$, $p < 0.001$) and fructosamine ($r = -0.555$, $p < 0.001$) while positively correlated to fasting C peptide ($r = 0.777$, $p = 0.002$).

Conclusions: Supplementation with zinc was well tolerated with no side effects were reported throughout the study. Zinc intake for 3 months represents a potential therapeutic adjuvant agent decreasing hyperglycemia, improving insulin secretion, glycemic control and increasing the efficacy of iron chelation therapy in reducing hemolysis, iron burden and elevating hemoglobin levels among pediatric patients with β -TM.

Bone, Growth Plate and Mineral Metabolism Session 1

RFC2.1

Burosumab resulted in better clinical outcomes than continuation with conventional therapy in both younger (1-4 years-old) and older (5-12 years-old) children with X-linked hypophosphatemia

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In children with X-linked hypophosphatemia (XLH), excess circulating fibroblast growth factor 23 (FGF23) causes hypophosphatemia with consequent rickets, skeletal deformities, and impairments in growth and mobility. Compared to

continuation with conventional therapy (oral phosphate and active vitamin D [Pi/D]), switching to treatment with burosomab, a fully human monoclonal antibody against FGF23, showed significantly greater improvement in phosphate homeostasis, rickets severity, lower limb deformity, growth, and mobility in children with XLH. Here, we report a sub-analysis from the Phase 3 Study CL301 (NCT02915705), comparing these treatment groups in children with XLH < and \geq 5 years-old.

Sixty-one children with XLH (1-12 years-old) were randomized 1:1 after a 7-day Pi/D washout to receive burosomab starting at 0.8 mg/kg SC Q2W or resume Pi/D titrated by their investigator. Eligibility criteria included Rickets Severity Score \geq 2.0 despite prior Pi/D treatment. Healing of rickets (primary endpoint) was assessed by radiologists blinded to treatment using the Radiographic Global Impression of Change (RGI-C) Score at Week 40. Lower limb deformity and growth were assessed at Week 64.

By Week 40, RGI-C score was significantly higher with burosomab than with Pi/D (LS mean \pm SE: burosomab, $+1.9 \pm 0.1$ versus Pi/D $+0.8 \pm 0.1$; $p < 0.0001$); RGI-C results were similar in subjects < 5 years-old (burosomab, n=14, $+1.9 \pm 0.2$ versus Pi/D, n=12, $+0.7 \pm 0.2$) and \geq 5 years-old (burosomab, n=15, $+2.0 \pm 0.1$ versus Pi/D, n=20, $+0.9 \pm 0.1$). Improvement in lower limb deformity score was greater with burosomab than Pi/D for all subjects (Week 64 LS mean \pm SE: $+1.3 \pm 0.2$ versus $+0.3 \pm 0.1$; $p < 0.0001$), subjects < 5 years-old ($+1.5 \pm 0.3$ versus $+0.5 \pm 0.2$), and subjects \geq 5 years-old ($+1.0 \pm 0.2$ versus $+0.1 \pm 0.1$). Burosomab showed greater improvement than Pi/D in length/height Z-score for all subjects (Week 64 LS mean change \pm SE: $+0.17 \pm 0.07$ versus $+0.02 \pm 0.04$; $p = 0.0490$), subjects < 5 years-old ($+0.15 \pm 0.12$ versus -0.05 ± 0.07), and subjects \geq 5 years-old ($+0.17 \pm 0.05$ versus $+0.08 \pm 0.04$). Dental adverse events (AEs) and AEs of interest identified from previous burosomab trials, including hypersensitivity and injection site reactions, were more frequent with burosomab, and were mild to moderate in severity overall. Three serious AEs occurred per group, all unrelated to treatment and resolved. No discontinuations occurred.

Both younger and older children with XLH demonstrated greater improvements in rickets, bowing, and growth during burosomab than those who continued with Pi/D.

RFC2.2

Does the treatment with recombinant human growth hormone improve final height in patients affected by X-linked hypophosphatemia?

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Background/Aim: 25 to 40% of children with well-controlled X-linked hypophosphatemia (XLH) show linear growth failure, despite optimal conventional treatment (oral phosphate supplementation and active forms of vitamin D) with final height -2 SDS. Recombinant human growth hormone (rhGH) may be an adjuvant treatment of the growth retardation in these patients. Therefore, the main objective of this study was to describe how rhGH treatment improves final height in children with XLH.

Materials/Methods: In our retrospective observational study we included children with XLH who received rhGH for at least one year and reached their final height. Final height was defined as age >16 years, or bone age > 16 years, or growth velocity <2 cm/year. We collected weight, height, and body mass index (BMI) at birth \rightarrow at XLH diagnosis \rightarrow at start of rhGH treatment \rightarrow 2 two years after rhGH treatment \rightarrow at the end of rhGH treatment \rightarrow at the last visit.

Results: 34 patients (13 male / 21 female) were included. Mean age at start of rhGH treatment was 9.8 ± 3.5 years. Duration of rhGH treatment and follow up were 3.4 ± 2.9 and 4.5 ± 3.1 years, respectively. The last visit was performed at 19.2 ± 3.4 years. Mean doses of rhGH at initiation and the end of treatment were 77.4 ± 14.5 and 66.8 ± 20.5 $\mu\text{g}/\text{kg}/\text{day}$, respectively. The average height of patients significantly increased from -2.4 ± 0.9 SDS at initiation, to -1.5 ± 0.7 SDS ($p < 0.001$) after 2 years of rhGH treatment, to -1.2 ± 0.9 SDS ($p = 0.67$) at rhGH discontinuation and to -1.3 ± 0.9 SDS at final height. The global height increment of rhGH was 1.2 ± 0.7 SDS.

Conclusion: Treatment with rhGH significantly increases final height SDS in comparison to pre-treatment height. Most height gain is obtained during the first 2 years of treatment and is sustained through final height despite treatment interruption.

	Diagnosis of XLH	Before rhGH	2 years after rhGH	End rhGH	Last visit
Age (Years)	3.4 ± 3.4	9.8 ± 3.5	11.9 ± 3.4	14.2 ± 3.1	19.2 ± 3.4
Height ((SDS))	-2.2 ± 1.2 0.887	-2.4 ± 0.9	-1.5 ± 0.7	-1.2 ± 0.9	-1.3 ± 0.9
P		0.001	0.670	0.996	

RFC2.3

Growth hormone effects on metacarpal bone geometry and bone age in growth hormone-deficient children

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Purpose: To track the effects of growth hormone on bone geometry and maturation in children with isolated growth hormone deficiency (GHD).

Methods: 299 left hand X-rays from 77 short prepubertal children (54 boys and 23 girls) with isolated GHD were analysed for changes in metacarpal thickness, width, length, medullary diameter, the Bone Health Index (BHI) and bone age (BA) from one year preceding until four years after start of GH treatment using BoneXpert, a fully automatic X-ray analysis software.

Results: Age-related standard deviation scores (SDS) revealed strong and significant stimulatory effects on thickness, length and width, ranking in this order, and no effect on medullary diameter. Height- and BA-related SDS also showed a significant increase in thickness, while length and width increased non-significantly in this regard. BHI increased for age, BA and height. Catch-up growth was strongest in the first year and, for BA, the more pronounced for a parameter the greater the baseline deficit was for that parameter. BA change was slower than change of thickness and height during the first year and thereafter faster, but BA remained delayed even after 4 years.

Conclusion: Children with isolated GHD have decreased metacarpal thickness and delayed bone age. GH treatment leads to a rapid normalisation of the former in the first year of treatment and a slow catch-up of the latter from the second year onwards.

Diagnoses were: astrocytic (G+2:n=25, G+5:n=24, G+7:n=20), embryonal (G+2:n=19, G+5:n=28, G+7:n=20), germinomas (G+2:n=13, G+5:n=18, G+7:n=12), sellar region (G+2:n=13, G+5:n=10, G+7:n=9), ependimal (G+2:n=3, G+5:n=7, G+7:n=5) tumors. Twenty-six, 37 and 27 pts, respectively, underwent CSRT in the 3 groups. Growth hormone deficiency (GHD) was diagnosed in 38(G+2), 66(G+5) and 46(G+7) pts, while hypogonadism (HH) in 15(G+2), 28(G+5) and 22(G+7) CBCS. Patients underwent height and BMI(SDS), pubertal(Tanner) and DXA(Lunar Prodigy Advance) measurements. BMD(g/cm²,Z-score), BMC(g) were obtained at the lumbar spine(L1-L4=L) and the total body less head(TB); lumbar BMAD(g/cm³) was calculated; fat(FM,Kg) and lean mass(LM,Kg) were obtained.

Results: The 3 groups had similar age at diagnosis (8,0±4,2yrs), height (-0,5±1,4SDS), BMI (0,7±1,2SDS); G+7 had higher FM and LM than G+2 and G+5 (FM:P's=0,01 and 0,003 respectively; LM:P's=0,0008 and 0,03). G+2 showed a reduced LBMD and LBMC compared to G+5 and G+7 (LBMD:P's=0,009 and <0,0001; for LBMC:P's=0,03 and 0,0003, respectively) and a non-significant lower LBMDZ-score (-0,85±1,33,-0,61±1,23 and -0,74±1,31) and TBBMDZ-score (-0,72±1,09,-0,59±1,04 and -0,51±1,14). BMAD was significantly higher (P=0,03) in G+7(0,157±0,083) compared to G+2(0,135±0,021). A LBMD<-2Z-score was present in 19,2%, 11,5% and 17,7% (G+2vsG+5vsG+7) and a TBBMD<-2Z-score in 14,1%, 11,9% and 12,5% (G+2vsG+5vsG+7). G+2GHD pts had lower LBMDZ-score(P=0,01) and TBBMDZ-score(P=0,04) compared to G+5GHD pts; G+2HH pts had lower LBMDZ-score and TBBMDZ-score compared to G+5HH (P=0,009 and 0,03, respectively). TBBMDZ-score progressively increased in pts not treated with CSRT, while remained below -0,9Z-score in treated-ones. In multivariable analyses LBMDZ-score was inversely predicted by age and directly by height after correction for LM, FM, GHD, HH; TBBMDZ-score was additionally predicted by LM and GHD. Seven% CBCS in G+2(5/73), 2,3% in G+5(2/87) and 1,5% in G+7(1/66) presented fractures.

Conclusions: Older, shorter, GHD, CSRT treated and HH CBCS are at risk of decreased BM after 2 yrs OT; a low BM might persist after 5 and 7 yrs OT; the fracture prevalence remains low.

RFC2.4

Bone Mass and Fracture Prevalence in Childhood

Brain Cancer Survivors 2, 5 or 7 years after off therapy

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Background and Aim: Multifaceted risk factors impair bone mass (BM) in childhood brain cancer survivors (CBCS). Aims of the study were to evaluate bone mass and its determinant and fracture prevalence in CBCS 2(G+2), 5(G+5) or 7(G+7) years after off therapy (OT).

Methods: Seventy-three(G+2), 87(G+5) and 66(G+7) CBCS were evaluated at 12, 9±4, 2, 14, 9±4, 4 and 16, 6±4, 4yrs, respectively.

RFC2.5

Long term effects of treatment with Oxandrolone (Ox) in addition to growth hormone (GH) in girls with Turner syndrome (TS) on bone mineral density in adulthood

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Introduction: Ox in a dose of 0.03-0.05 mg/kg per day in addition to GH treatment significantly increases adult height in TS

more than GH alone. To date, the long term effects of Ox in childhood on bone mineral density (BMD) in adulthood are unknown.

Methods: This is a follow-up study of a previous randomized controlled trial, performed in the Netherlands. In the original trial, 133 girls were treated with GH, Placebo (Pl), Ox 0.03, or Ox 0.06 was added to GH when the age of 8 years was reached. Estrogens started from 12 years of age following a standard pubertal induction scheme. GH and Ox were stopped after adult height was reached. 66 women participated in the double-blind follow-up study (Pl, n=21; Ox 0.03, n=27; Ox 0.06, n=18). Mean age, 24.0 years; mean time since stopping GH, 8.7 years; and mean time of Ox/Pl use, 4.9 years. BMD of the lumbar spine, femoral neck and total body were assessed using dual-energy X-ray absorptiometry (DXA) scans (QDR 4500 densitometer, Hologic). Mean Z-scores were calculated and compared between Ox dose groups using ANOVA. In addition, mean Z-scores were compared to reference values of healthy women using t-tests.

Results: In the Pl group BMD Z-score of the lumbar spine (-0.82), femoral neck (-0.74) and total body (-0.63) were significantly lower ($p < 0.005$) compared to healthy women. In the Ox 0.03 group only the BMD Z-score of the lumbar spine and in the Ox 0.06 the BMD of the femoral neck were significantly lower than healthy individuals. BMD Z-score of the lumbar spine was significantly higher in girls treated with Ox (Ox 0.03: -0.32; Ox 0.06: -0.08) compared to girls treated with Pl (-0.82, $p = .014$), without significant difference between dose treatment groups. Although there was a trend towards a higher BMD Z-score of the femoral neck (Pl: -0.74; Ox 0.03: -0.22; Ox 0.06: -0.49) and total body (Pl: -0.63; Ox 0.03: -0.21; Ox 0.06: -0.24) in the Ox groups compared to Pl, no significant differences were found.

Conclusions: DXA Hologic scans in adult TS treated with GH in childhood show a lower BMD, not adjusted for height, than healthy individuals of the same age. The addition of Ox to GH in childhood results in a significantly higher lumbar spine BMD than GH alone, with a similar trend for the femoral neck and total body. No significant differences were found between Ox 0.03 and Ox 0.06.

Methods: Thirty-eight adolescents (32/38 assigned females at birth) with GD had dual energy X-ray absorptiometry (DXA) prior to starting GnRH analogue and after one year of therapy. DXA lean mass index (LMI: defined as DXA lean mass/height²) and fat mass index (FMI: defined as DXA fat mass/height²) were converted to Z-scores based on LMI and FMI centiles from a cohort of healthy school children from Glasgow. DXA total body less head bone mineral content (TBLH-BMC) and DXA lumbar spine bone mineral apparent density (LS-BMAD) were converted to Z-scores based on published UK normative data. TBLH-BMC was adjusted for lean mass, fat mass, height, age and ethnic background.

Results: Median age at baseline was 14.2 years (10.6, 15.7) with 33/38 (87%) being in late puberty (Tanner IV and V). Median body mass index (BMI) Z-score, at baseline and after one year of treatment, was +0.9 (-1.7, +3.4) and +1.4 (-0.8, +3.5), respectively [$p < 0.0001$]. Median FMI Z-score, at baseline and at one year, was +0.8 (-1.1, +2.1) and +1.0 (-0.1, +3.2), respectively [$p < 0.0001$]. Median LMI Z-score was -0.6 (-2.8, +2.6) at baseline, and -0.7 (-3.6, +1.5) at follow-up [$p < 0.0001$]. Twelve months of pubertal suppression led to a reduction of LS-BMAD Z-score, from a median of -0.1 (-2.2, +2.3) at baseline to a median of -0.5 (-2.7, +1.8) at one year [$p < 0.0001$]. Similarly, median TBLH-BMC Z-score was +0.4 (-2.6, +3.6) at baseline, and +0.2 (-2.8, +2.9) at follow-up, [$p = 0.03$]. LS-BMAD Z-score was positively associated with LMI Z-score at baseline [$r = 0.43, p = 0.007$] and at follow up ($r = 0.47, p = 0.003$). In those adolescents (n,8) who showed a reduction of >1.0 SD in LS-BMAD Z-score between baseline and one year, median change in LMI Z-score was -1.1 (-1.5, +0.2) compared to the median change in LMI Z-score of -0.2 (-1.2, +2.7) in those with a reduction of <1.0 SD in LS-BMAD Z-score between [$p = 0.003$].

Conclusion: Adolescents with GD have relatively low lean mass and relatively high fat mass at baseline. After one year of treatment with GnRH analogue, they showed further reduction in lean mass, an increase in fat mass and a reduction in bone mineral density, at both lumbar spine and total body.

RFC2.6

Impact of Pubertal Suppression on Body Composition and Bone Mineral Density in Adolescents with Gender Dysphoria

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Introduction: Pubertal suppression with gonadotrophin releasing hormone (GnRH) analogue is introduced after the onset of puberty in adolescents with gender dysphoria (GD). As puberty is a critical period for bone accrual and changes in body composition, alterations in body composition and bone mass may be observed during treatment.

Multi-System Endocrine Disorders

RFC3.1

European Registries For Rare Endocrine Conditions (EuRRECa): Results From The Pilot Phase Of The Platform For e-Reporting Of Rare Endocrine Conditions (e-REC)

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Background: EuRRECa (European Registries for Rare Endocrine Conditions) is a new project incorporating the development of a core endocrine registry and the development of an e-reporting programme for rare endocrine conditions (e-REC) that are covered within Endo-ERN (<https://eurreca.net/e-rec/>).

Methods: 24 Endo-ERN centres within 12 countries participated in a pilot phase of e-REC from July 2018 to December 2018. An electronic reporting ‘card’ developed through Redcap was issued monthly to enquire whether clinicians had encountered a new case of any conditions within the eight Endo-ERN main thematic groups (MTGs).

Results: 23 centres were invited to report on paediatric cases and 24 centres were invited to report on adult cases. Of these, a median of 15 (range 12, 16) paediatric centres and 13 (12, 14) adult centres actively reported cases and a median of 44 (27, 75) paediatric cases and 83 (42, 120) adult cases were reported on a monthly basis. Amongst paediatric cases, conditions within the Sex Development, Thyroid and Pituitary MTGs were most commonly reported comprising 41%, 15% and 12% of all reported conditions, respectively. Amongst adult cases, conditions within Pituitary, Thyroid and Adrenal MTGs were most commonly reported, making up 41%, 19% and 10% of conditions, respectively. In children, the median number of cases reported per centre over a 6-month period was 17 (9, 32) for conditions affecting Sex Development, 6 (3, 11) for Thyroid disorders and 5 (3, 9) for Pituitary disorders. In adults, for the most commonly reported conditions, the median number of cases reported per centre were 35 (16, 44), 16 (5, 24) and 8 (1, 22) for Pituitary, Thyroid and Adrenal MTGs respectively.

Conclusion: The e-REC platform can be used to capture information on new encounters with patients with rare endocrine conditions. Results from the pilot phase of e-REC show a wide variability in the number of patients with specific groups of rare conditions that are encountered in the paediatric and adult settings and following the pilot phase, the platform has now been launched for general use. It is anticipated that the outputs from this project will be of interest to a wide range of stakeholders.

RFC3.2

Factors affecting loss to follow-up for patients with chronic endocrine conditions during the pediatric period: a cohort study at a reference center for rare diseases

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Introduction: Most patients with endocrine diseases diagnosed during childhood require long-term continuity of care. A lack of regular medical follow-up visits may be associated with impaired long-term health outcomes, with greater risks of morbidity and mortality. The importance and challenges of the transition from pediatric to adult healthcare are well recognized, but few studies have considered loss to follow-up during pediatric care. We investigated the prevalence of patients with chronic endocrine disease lost to follow-up (LTFU) during the pediatric period, to identify risk factors associated with LTFU.

Patients and Methods: This observational cohort study included all patients under the age of 16 years with chronic endocrine diseases included in the database of a single academic pediatric care center between January 2007 and June 2014, with a study end point in December 2016. Patients who had not attended clinical visits for over two years, for unknown reasons, were considered LTFU. Of the 1463 patients, 396 stopped attending the clinic for known reasons. All patients resident in France were covered by the national health insurance system, including those classified as having a low income (18% of our cohort).

Results: Of the 1067 remaining patients, 154 (14%) were LTFU. Median (25-75th percentile) age at diagnosis was 5.8 (0.3-11.8) vs. 1.2 (0.0-6.8) years, age at the last visit was 14.1 (9.7-16.2) vs. 11.7 (6.1-15.8) years, median follow-up was 4.3 (1.9-9.1) vs. 6.1 (3.5-10.1) years at the end of the study period and the number of visits during the last three years was 4.0 (3.0-6.0) vs. 6.0 (4.0-7.0) for patients LTFU and patients not LTFU, respectively.

In multivariate analysis, the risk of being LTFU increased with age at diagnosis (OR 1.18; 95%CI: 1.12-1.24), diagnosis before 2006 (vs. after 2006) (OR 4.80; 3.00-7.66), smaller numbers of visits in the last three years (OR 0.72; 0.65-0.80); ($p<0.0001$), and lower health insurance classification (OR 1.79; 1.10-2.89; $p=0.02$). Patients with isolated GH deficiency were at higher risk of being LTFU than those with other endocrine conditions, such as thyroid, gonadal, adrenal, or multiple pituitary deficiencies, or Turner's syndrome (OR 5.24; 1.13-24.37; $p=0.03$).

In conclusion: This study is the first to provide epidemiological data on children and adolescents with pediatric endocrine chronic diseases LTFU. It should help to target interventions for improving adherence to medical care and improvements in healthcare organization during the pediatric period.

RFC3.3

The Founder Homozygous NR5A1 Gene Mutation p.R103Q Causes Asplenia and Severe XY-DSD and XX-DSD in a Palestinian Cohort

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Background: Mutations in Steroidogenic factor 1 (*SF-1*; also known as *NR5A1*), a transcription factor involved in sexual differentiation, steroidogenesis and reproduction, have been associated with mild to severe XY and XX DSDs and adrenal failure. Asplenia and complete XY sex reversal were recently reported in a Palestinian patient homozygous for p.R103Q *NR5A1* mutation.

Clinical Cases: Five Palestinian girls (three 46, XY and two 46, XX) from 3 unrelated families presented between 13-15 years

of age with absence of spontaneous pubertal development and primary amenorrhea for investigations. Three cases had 46, XY karyotype and female external genitalia. They had a significant history for infectious diseases (e.g. pneumococcal sepsis at 9 months of age, aseptic meningitis, hepatitis A, suppurative hip arthritis), asplenia, bilateral inguinal dysgenetic or absent testes, rudimentary or absent uterus and undetectable AMH levels. The 2 other cases (sisters) had 46, XX karyotype, hyposplenia, infantile uterus, absence of ovaries in imaging studies and undetected serum AMH.

Asplenia was recognized only lately in all of the cases except for case 4, where it was diagnosed at age of 6 months. Interestingly case 2 exemplified delayed adrenarche and undetectable levels of Dehydroepiandrosterone, androstenedione, and testosterone.

All five cases had the homozygous *NR5A1* p.R103Q mutation, originating from one founder. (1).

Conclusions: The homozygous R103Q *NR5A1* mutation causes complete XY sex reversal but also completely disables the development of an ovary. DSD in the context of significant infections should alert to asplenia and *NR5A1* mutation, and consequently indicate lifesaving preventive measures such as vaccinations and antibiotic prophylaxis. The undetectable AMH levels in this cohort suggests a critical role of human SF-1 in AMH transcription. The delayed adrenarche, and the undetected serum androgens levels in case 2 proves that SF-1 is required for CYP17A1 transcription. The presence of Mullerian structures in this case is the most severe reported XY DSD phenotype of *NR5A1* mutation.

Reference

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RFC3.4

Peripheral glucocorticoid metabolism may reflect resolution of inflammation in Kawasaki disease

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Background: Kawasaki disease (KD) is an acute inflammatory disorder, associated with systemic vasculitis including coronary artery aneurysms (CAA). Treatment with intravenous immunoglobulin (IVIG) can resolve inflammation. However, about 20% patients show resistant to IVIG treatment and some of the cases required additional treatments. Recently, IVIG plus adjuvant glucocorticoid hormones (GC) has been shown to be an effective therapy for these patients, suggesting that GC may complement IVIG treatment in IVIG resistant-KD. We hypothesized that failure to appropriately regulate endogenous GC signaling may contribute to persistent inflammation in KD. Intracellular GC levels in peripheral tissues are controlled by pre-receptor metabolism by 11beta-hydroxysteroid dehydrogenase (11b-HSD). 11b-HSD1 converts intrinsically inert cortisone to active cortisol, increasing GC levels available to activate glucocorticoid receptor (GR).

Objective: The aim of this study was to establish if 11b-HSD1 in PBMC is associated with IVIG sensitivity in KD.

Methods: Levels of 11b-HSD1 and GR mRNA were measured in peripheral blood mononuclear cells (PBMC) isolated from all children diagnosed with KD at Teine-Keijinkai Hospital, Sapporo, Japan between April 2015 and January 2018 (a total of 31). IVIG was initiated in all patients on day 5 or 6 after the onset of high fever. Nineteen patients were classified as IVIG-sensitive patients, who showed complete resolution of high fever after initial IVIG treatment. Twelve patients were classified as IVIG-resistant due to persistent fever. Peripheral blood samples were obtained before and after IVIG treatment with informed consent. RNA was extracted from PBMC. 11b-HSD1 and GR mRNA levels were measured by qRT-PCR.

Results: There was no significant difference in the basal levels of 11b-HSD1 and GR mRNA between IVIG-sensitive and –resistant KD. However, following IVIG treatment, 11b-HSD1 mRNA levels were significantly increased in IVIG-sensitive KD, but not in IVIG-resistant KD. There was no significant effect of IVIG treatment on GR mRNA levels in either group.

Conclusions: Increased 11b-HSD1 activity in PBMC is predicted to increase the intracellular levels of cortisol generated from cortisone, thereby amplifying intracellular GC-mediated attenuation of proinflammatory cytokine action in PBMC of IVIG-sensitive KD. In contrast, the failure to up-regulate 11b-HSD1 in PBMC in IVIG-resistant KD patients might contribute to the persistence of inflammation. Understanding the role of endogenous glucocorticoid signaling in immune cells during the course of KD may highlight future possible therapeutic avenues to treat IVIG-resistant KD.

Methods: Anthropometric parameters [height (H), body mass index (BMI), waist circumference (WC), hip circumference (HC), WC/H and WC/HC ratio], blood pressure, glucose and lipid profile, serum CV markers [Interleukin 6 (IL-6), Vascular Cell Adhesion Molecule (VCAM), Intercellular Adhesion Molecule (ICAM), Tumor Necrosis Factor-alfa (TNF- α), Endogenous secretory Receptor for Advanced Glycation Endproducts (Es-RAGE)] and ultrasound parameters of endothelial function (carotid intima-media thickness, c-IMT) were assessed in 28 ALL survivors (71% male, 18% prepubertal, aged 15.98 ± 4.41 years) at least two years after the end of chemotherapy (mean follow-up 8.57 ± 3.14 years) and in 22 sex- and age-matched controls (64% male, aged 16.59 ± 5.60 years).

Results: ALL survivors exhibited low levels of Es-RAGE than controls (0.18 ± 0.07 vs. 0.27 ± 0.08 ng/ml, $p < 0.001$). No other differences in serum CV markers were detected between survivors and controls. Among survivors, Es-RAGE values significantly correlated with BMI-SDS off-therapy ($R^2 = 0.42$), WC/H ratio ($R^2 = 0.41$), WC/HC ratio ($R^2 = 0.38$) and with low-density-lipoprotein cholesterol (LDL-c; $R^2 = 0.43$). IL-6 and TNF- α levels directly correlated with WC/H ratio ($R = 0.41$), WC/HC ratio ($R = 0.51$), triglycerides values ($R = 0.40$) and with diastolic blood pressure (DBP; $R = 0.50$), respectively. Moreover, in ALL survivors, mean c-IMT was within the normal range for age (0.55 ± 0.14 mm, range 0.4–0.85) and correlated with systolic blood pressure (SBP; $R = 0.56$), DBP ($R = 0.66$) and LDL-c levels ($R = 0.56$). According to Weiss' definition, metabolic syndrome (MetS) was fully detected only in one ALL survivor. Nevertheless, 18% ALL survivors presented more than one MetS diagnostic criteria: 14% showed insulin-resistance, 25% dyslipidemia and 17.8% hypertension.

Conclusions: We demonstrated that in ALL survivors, as in general population, all the investigated CV markers correlate with modifiable clinical and biochemical parameters. Therefore, a healthy lifestyle should be encouraged soon after chemotherapy. The detection of low levels of Es-RAGE in ALL survivors could be due to their consumption in a chronic endothelial inflammatory condition that seems to be only partially reversible after chemotherapy.

RFC3.5

Evaluation of endothelial function in childhood standard risk acute lymphoblastic leukemia survivors: role of subclinical markers and identification of preventable factors

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Background: Adult survivors from childhood malignancy are prone to accelerated atherogenesis and cardiovascular (CV) complications. In this population reliable tools are needed to detect preclinical onset of CV disease.

Aim: To assess subclinical markers of inflammation and endothelial dysfunction in young survivors from acute lymphoblastic leukemia (ALL) treated with chemotherapy without cranial irradiation (AIEOP 2000 and 2009 standard risk protocols).

RFC3.6

Prevalence of endocrine complications in Duchenne muscular dystrophy

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Background: Duchenne muscular dystrophy (DMD) is caused by mutations in the dystrophin gene and results in a progressive muscular damage and degeneration. Endocrine complications result from decreased energy expenditure, immobility and

glucocorticoid (GC) treatment. Due to the multidisciplinary management and emerging genetic and molecular therapies longer survival is expected and there is an increasing emphasis on the quality of life in DMD. Aim of the study was to determine prevalence of selected endocrine complications in a national cohort of boys with DMD treated or not with GC.

Methods: 29 boys with DMD (age (mean \pm SD) 11.5 \pm 5.4 years) were studied at annual multidisciplinary visit. Levels of IGF-1, IGF-BP3, TSH, free T4, glucose, insulin and vitamin D3 were determined in the morning following an overnight fast. Bone mineral density and body composition were determined by DEXA. Data were expressed as mean \pm SD, groups were compared by T-test, correlations were made by Pearson's coefficient. P-values < 0.05 were considered statistically significant.

Results: 13/29 received GC (deflazacort) for 3.6 \pm 3.1 year (starting at 6.9 \pm 8.4 years). 7/29 were short stature (2 in GC group), 1/29 (0 in GC group) was underweight and 6/29 (3 in GC group) were overweight. HOMA-IR was increased in 8/29 (5 in GC group), none had impaired glucose tolerance or diabetes. No cases of acute adrenal insufficiency were reported. Lumbar spine-BMD was decreased in 8/29 (3 in GC group), 24/29 received vitamin D3 supplements and one subject needed antiresorptive therapy.

There were no differences in the mean values of selected parameters between those receiving or not-receiving GC. Glucocorticoid treatment duration however correlated positively with BMI-SDS and % fat mass ($r=0.722$, $p=$ and $r=0.84$, $p=.018$ respectively) and negatively with % lean mass (-.88, $p=.004$).

Conclusions: Short stature, under and overweight, insulin resistance and decreased BMD are common however not obligatory endocrine complications in DMD. Although there were no differences in studied parameters between those receiving and not-receiving GC, there was a positive correlation between GC treatment duration and BMI-SDS and increased fat mass confirming GC as a risk factor for possible metabolic complications in DMD.

Fat Metabolism and Obesity Session

RFC4.1

Expression of miRNAs in circulating exosomes derived from patients with NAFLD

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Nonalcoholic fatty liver disease (NAFLD), which represents the leading cause of hepatic damage worldwide, is modulated by epigenetic factors, in particular microRNAs (miRNAs), which control at post-transcriptional level many complementary target mRNA. However, the evidence for this is inconsistent. The high stability and expression of circulating exosomal miRNAs may allow their use as candidate biomarkers. For the discovery phase, exosomes were isolated from the serum of patients with obesity as the controls (n=5) and obesity&NAFLD (n=5) for microarray analysis

of miRNAs. Thirty miRNAs were expressed significantly higher (>1.5-fold) in patients with obesity&NAFLD, but not in patients with obesity. Notably, expression of 5 miRNAs (miRNA-122-5p, -3591-3p, -1290, -23a-5p, and let-7g-3p) was elevated by more than 4.5-fold in patients with obesity&NAFLD. For the validation phase, miRNAs were analyzed using quantitative RT-PCR analysis in exosomes from the serum of patients with obesity control (n=20) and patients with obesity&NAFLD (n=20). These miRNAs and their target genes may regulate a wide spectrum of biological processes and metabolic homeostasis, including lipid synthesis, fatty acids and glucose catabolism, inflammation, proliferation, apoptosis and necrosis, which have been known to be epigenetically deregulated in NAFLD. These findings suggest that serum exosomal miRNAs might be used as novel biomarkers to reflect the progression of NAFLD.

RFC4.2

Circulating Exosomal miRNAs in Children's Nonalcoholic Steatohepatitis and the Correlation with Serum Transaminase and Uric Acid

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Background: The incidence of non-alcoholic fatty liver disease (NAFLD) in children increased rapidly paralleled with the global burden of obesity and diabetes. Although most patients are non-alcoholic fatty liver (NAFL), once progress to nonalcoholic steatohepatitis (NASH), the risk of liver fibrosis and cirrhosis increase significantly. However, the pathogenesis of NAFLD, especially how NAFL progress to NASH is still unclear. Exosomal miRNAs have attracted attention to provide further insights into the pathogenesis of NASH, and it may also serve as biomarkers of NASH.

Methods: Children diagnosed as NASH (n=20) and age matched health control (n=20) were enrolled in this study. They were randomly divided into test set (3 NASH/3Controls) and validation set (17 NASH/17Controls). Circulating exosomes were isolated from both sets according to the protocol of the miRCURY Exosome Serum/Plasma Kit. For the test set, Illumina HiSeqTM 2500 was performed to analyze the differential expression of exosomal miRNAs between the two groups; bioinformatics analysis was applied to identify the molecular signature differences. The differentially expressed miRNAs were further validated in the validation set. ANOVA analysis was used to compare the clinical parameters between the NASH and control group. Spearman correlation analysis was used to investigate the association between differential miRNAs and indicators of body fat, inflammation, glucose and lipid metabolism.

Results: Exosomes were validated by NTA and flow cytometry (CD81 and CD63). With Illumina HiSeqTM 2500, 40 miRNAs were differentially expressed ($| \log_2(\text{fold change}) | \geq 1$, $P < 0.05$) in the test set. Gene Ontology (GO) annotation and Pathway analysis revealed that the differential miRNAs were involved in lipid metabolism, insulin signaling, apoptosis and inflammation pathway.

Among which, miRNA122, miRNA34a, miRNA155 and miRNA146b-3p were up-regulated significantly in NASH group than the control Group ($P<0.05$). The weight, BMI, Uric Acid, serum ALT and AST were significantly higher in NASH group than the control group ($P<0.05$). miRNA122, miRNA34a, miRNA155 and miRNA146b-3p were positively correlated with BMI ($r, 0.41-0.59$), ALT ($r, 0.36-0.52$), AST ($r, 0.31-0.48$) and Uric Acid (UA, $r, 0.51-0.69$) ($P<0.05$). And there is no relationship between the miRNAs with triglyceride and cholesterol.

Conclusions: Circulating exosomal miRNA122, miRNA34a, miRNA155 and miRNA146b-3p were up-regulated in NASH group, and positively correlated with serum transaminase and UA. So the exosome derived miRNAs may involve in the pathogenesis of NASH and can be used as a potential biomarker for diagnosis of children NASH.

RFC4.3

Dysregulated gene expression profile in visceral adipose tissue of juvenile *Wistar* rats with catch-up growth: association with fat expansion and metabolic parameters

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Background: Accelerated catch-up growth following intrauterine growth restriction increases the risk of developing visceral adiposity and metabolic syndrome. Animal models of growth restriction during gestation have been developed as a powerful tool to provide insight into the underlying molecular mechanisms thereof.

Objective: To analyze the patterns of gene expression in the retroperitoneal adipose tissue of rats with intrauterine growth restriction and postnatal catch-up growth.

Methods: A *Wistar* rat model of catch-up growth following intrauterine growth restriction was used. Dams fed *ad libitum* delivered control pups (C) and dams on a 50% calorie-restricted diet during gestation delivered pups with low birth weight (R). Restricted offspring fed a standard rat chow showed catch-up growth (RC) but those kept on a calorie-restricted diet did not (RR). Microarray studies were performed in the retroperitoneal adipose tissue of postnatal day 42. Among the top twenty ranked genes with the highest fold change between RC and RR, yielded by microarray, we selected five genes to be validated by qRT-PCR.

Results: Of the total number of genes ($n=23,188$), we identified 570 as differentially expressed genes (Fold Change $> 3\log_2$) in the retroperitoneal adipose tissue of RC vs RR (FDR-p value <0.05).

Functional enrichment analysis revealed a global upregulation of genes involved in carbohydrate and lipid metabolism and a down-regulation of genes linked to inflammation and immune response. Five genes representative of these main pathways (*Npr3*, regulation of blood pressure; *Pnpla3*, lipid metabolic processes; *Slc2a4*, brown fat cell differentiation; *Serpina3n*, inflammatory response; *Serpina12*, positive regulation of PI3K) were confirmed by qRT-PCR and showed associations with several metabolic parameters, including body weight, amount of brown adipose tissue, and serum insulin and lipids.

Conclusion: We have identified the differential expression pattern in visceral adipose tissue of juvenile *Wistar* rats with catch-up growth following intrauterine growth restriction. We suggest that the differential regulation of these genes may be involved in visceral fat expansion during catch-up growth in juvenile rats and in the predisposition of these animals to develop metabolic abnormalities.

RFC4.4

The novel phosphatidylinositol-3-kinase (PI3K) inhibitor alpelisib effectively inhibits growth of PTEN haploinsufficient lipoma cells

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Background and Aim: Germline mutations in the tumor suppressor gene PTEN cause PTEN Hamartoma Tumor Syndrome (PHTS). Pediatric patients frequently develop lipomas. PTEN antagonizes the growth promoting PI3K/AKT/mTOR pathway. There is no current treatment option except surgery. Treatment attempts with the mTORC1 inhibitor Rapamycin could not reverse lipoma growth. Recently, lipomas associated with a related syndrome caused by mosaic activating PI3K mutations (PIK3CA-related overgrowth syndrome, PROS) were successfully treated with the novel PI3K inhibitor alpelisib. Here we tested whether or not alpelisib has growth restrictive effects and induces apoptosis in lipoma cells from a pediatric patient with PHTS

Methods: We used PTEN haploinsufficient lipoma cells (LipPD1) and treated them with alpelisib alone or in combination with rapamycin. We tested viability, proliferation, apoptosis and signaling in those cells at different alpelisib concentrations (0.1–100 μ M).

Results: Alpelisib reduced the viability of LipPD1 cells in a concentration- ($p<0.0001$) and time- ($p < 0.0001$) dependent manner as shown by WST-1 assays after 24, 48, 72, 96, 120 and 144 h. After 48 h cell count was decreased (0.75 fold at 10 μ M, $p = 0.0001$), as well as the fraction of the proliferation marker Ki-67 positive cells (0.45 fold at 10 μ M, $p=0.0346$). A combination with 10 nM rapamycin decreased cell viability further (0.76 fold after 72 h, $p=0.0283$). After 24 h Annexin V/Propidium iodide apoptosis assay was negative. Western blots revealed a reduced phosphorylation of AKT

(0.06 fold at 100 μ M), mTOR (0.59 fold at 100 μ M) and ribosomal protein S6 (0.5 fold at 100 μ M) in the alpelisib treated cells. While rapamycin treatment alone led to decreased levels of mTOR phosphorylation (0.43 fold at 10 nM), the AKT phosphorylation was increased (9.33 fold at 10 nM). This effect could be reversed by combining rapamycin with 100 μ M alpelisib (0.22 fold compared to solvent control).

Discussion: The reduced activation of AKT through inhibition of PI3K with alpelisib reduced cell viability and proliferation of PTEN deficient lipoma cells. After 24 h treatment we did not observe apoptosis, but later time points remain to be tested. Rapamycin activated AKT through a negative feedback loop which was prevented by simultaneous treatment with alpelisib.

Conclusion: Since alpelisib was well tolerated in first clinical trials, this drug could be a potential new treatment for PHTS-related adipose tissue hyperplasia.

RFC4.5

GDF5 Increased White Adipose Tissue Thermogenesis Through p38 MAPK Signaling Pathway in Fatty Acid-binding Protein 4-GDF5 Transgenic Mice

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Growth differentiation factor 5 (GDF5) was reported to regulate brown adipogenesis, however, its effects on insulin sensitivity, full metabolic syndrome spectrum and the thermogenesis in subcutaneous white adipose tissue (sWAT) haven't been elucidated yet. We thus generated fatty acid-binding protein 4 (Fabp4)-GDF5 transgenic mice and showed that GDF5 transgenic mice developed a relative lean phenotype on a high-fat diet (HFD) and showed increased insulin sensitivity. Over expression of GDF5 in adipose tissues greatly promoted the thermogenic process in sWAT following cold or β 3-agonist treatment. In transgenic mice, sWAT showed an important thermogenic effect as the thermogenic gene expression was markedly increased, which was consistent with the typical features of beige adipocytes. Enhanced MAPK/ATF2 signaling was also identified in sWAT of HFD-fed GDF5 mice, and thermogenesis in mature adipocytes induced by GDF5 protein could be partly blocked by a p38 MAPK inhibitor. Taken together, our data suggest that GDF5 could improve insulin sensitivity and prevent metabolic syndrome, the adaptive thermogenesis in sWAT could mediate the obesity resistance effects of GDF5 in mice and partially resulted in the activation of the p38 MAPK signaling pathway.

RFC4.6

Appetite Suppressing Effects of Glucoregulatory Peptides Devoid of Nausea

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Few treatments for type 2 diabetes (T2D) and obesity achieve meaningful long-term weight-loss and are often accompanied by nausea and vomiting. Thus, there is a critical need for a new generation of obesity medications that provide glycemic control with enhanced hypophagic response without nausea. Our group has developed and tested two new monomeric chimeric peptides against a novel target for obesity treatment concomitant with T2D in the form of dual agonism of the anorectic neuropeptide Y2-receptor (Y2-R) and the glucoregulatory glucagon-like peptide 1-receptor (GLP-1R). Using rational design and *in silico* modelling based on the GLP-1R agonist (GLP-1RA) exendin-4 (Ex-4) and the Y2-R agonist PYY(3-36), we developed two novel chimeric peptides, EP44 and GEP44. Both peptides bind and robustly activate the GLP-1R as well as the Y2-R, as assessed by cell-based fluorescence resonance energy transfer assays used to screen designed peptides for dose dependent receptor agonism (GLP-1R agonism EC₅₀: EP44 240 pM, GEP44 300 pM, Ex-4 23 pM; Y2-R agonism EC₅₀: EP44 32 nM, GEP44 10 nM, native PYY₃₋₃₆ 16 nM). We found that EP44 and GEP44 both robustly stimulate the insulin secretion rate in rat islet perfusion *in vitro*. EP44 potently reduced glucose levels during glucose tolerance tests in rats *in vivo* (30 min glucose: 269±14 mg/dL pre-treatment, 181±16 mg/dL after five once-daily 10 nmol/kg EP44 doses, p<0.001). Furthermore, we tested effects of daily injections of these chimeric peptides in adult Sprague-Dawley rats on food intake (FI), body weight (BW) changes, blood glucose levels and kaolin intake, the latter as an indicator of nausea. Both peptides reduced FI, with GEP44 producing profound reduction in FI (2-d average EP44 at 30 nmol/kg FI -15%; GEP44 at 20 nmol/kg FI -71%; Ex-4 20 nmol/kg FI -40%). Of note, anorectic doses of EP44 or GEP44 did not trigger kaolin consumption in treated rats, while in Ex-4 treated rats, kaolin consumption accounted for 28% of total daily solid intake, indicating a clear nausea response. During 11 d of treatment with GEP44, FI was consistently reduced resulting in a significantly stronger reduction of BW compared to Ex-4 at the end of treatment (GEP44 -7.6%, Ex-4 -3.7%). In conclusion, utilizing a novel concept of targeting serial anorectic pathways simultaneously with single-small chimeric peptides developed by our group is a new strategy addressing two coexisting conditions, namely obesity and T2D, to safely reduce FI, BW and blood glucose levels.

Thyroid

RFC5.1

Hurthle cell carcinoma in childhood: Retrospective analysis of a large series

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Background: In general population Hurthle cell cancer (HCC) accounts for 3-7% of all differentiated thyroid cancers (TC) with a more aggressive course, while its relative prevalence and behavior in childhood is uncertain due to the lack of specific literature reviews.

Objective: To describe the largest pediatric HCC cohort to date reported and to estimate its relative prevalence among TC variants in childhood.

Methods: Study population included 5 patients <19 years, who were diagnosed with HCC during the period 2000-2018 in our Departments. Histologic diagnosis of HCC was based on the finding of at least 75% of Hurthle cells at post-surgical analysis. HCC course was retrospectively reconstructed with data recorded at diagnosis, at surgical resection and during a follow-up period ranging from 6.5 to 15 years. Patients' assessment included: clinical findings, thyroid function and autoimmunity tests, neck and chest imaging (ultrasound and computed tomography scan), cytologic and histologic analyses of the tumor.

Results: HCC occurred with a relative prevalence of 5.8% (5 of 86 young patients affected by TC, diagnosed in the same period and institutions), at a median chronological age of 12.5 years. All patients were biochemically euthyroid at HCC diagnosis and underwent both total thyroidectomy with central neck dissection and radioiodine therapy, with subsequent L-T4 thyroidal suppression. Low or intermediate risk level was observed at diagnosis, since none of our patients exhibited extensive lateral neck disease or distant metastases and all of them showed a persistent clinical, biochemical and imaging remission over time. Antecedents of other diseases were recorded in 3 patients (Hashimoto's thyroiditis, Neurofibromatosis type 1 and osteosarcoma respectively).

Conclusions: 1) in childhood the relative prevalence of HCC among TC histotypes is 5.8%, that is close to the one reported from literature both in general population (3-5.7%) and in young patients (2-7%); 2) HCC may develop even very early, at an age of 7 years; 3) in pediatric age HCC does not seem to have a more aggressive behavior than other TC histotypes; 4) antecedents of other diseases are not infrequent in the history of children with HCC.

RFC5.2

Ultrasound features of multinodular goiter in DICER1 syndrome

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Background: DICER1 syndrome is caused by germline mutations in the *DICER1* gene. It is associated with a wide spectrum of benign and malignant neoplasms, which are accompanied by specific somatic mutations in *DICER1*. Multinodular goiter (MNG) is a common clinical feature of DICER1 syndrome in children and adults; the thyroid ultrasound (US) features of MNG in the setting of DICER1 syndrome have not been widely reported.

Objective: The aim of this study is to determine the US characteristics of MNG in patients with DICER1 syndrome.

Materials and Methods: This retrospective study evaluated thyroid ultrasound studies performed between 2011 and 2018 at a single centre. Patients ≤18 years with *DICER1* germline mutations and an intact thyroid gland were identified and included. Mutation-positive parents without previous thyroidectomy were also included. All studies were performed by the same pediatric endocrinologist and were subsequently re-examined by an independent radiologist from another academic center. The architecture of lesions was characterized as: simple cyst, septated cyst, mixed cystic and solid, or solid. US phenotypes of MNG in the setting of *DICER1* mutations were compared with known US features of thyroid malignancy. All mutations in *DICER1* were identified in a single research laboratory and confirmed via orthogonal techniques.

Results: Thirteen *DICER1* mutation-positive persons were identified (10 children, 3 adults). Three children had a normal thyroid ultrasound; therefore, thyroid abnormalities were assessed in 7 children and 3 adults. In both children and adults, mixed cystic and solid nodules predominated. We did, however, observe also single cystic, single cystic septated and single solid nodules. Solid lesions were present in 9 of 10 patients but all were isoechoic and without detectable intranodular blood flow except in one patient with multiple solid nodules. Other findings that are characteristic for MNG in DICER1 syndrome were as follows: multiple lesions (≥3) in all examined patients occasionally with a "spoke-like" presentation, absent vascular flow on Power/Color Doppler (except 1 patient), and macrocalcifications were present in all three adults.

Conclusions: The spectrum of US findings of MNG in *DICER1* mutation-positive patients is characteristic and is largely distinct from typical features of thyroid malignancy. Observed patterns include: multiple lesions (≥3), mixed cystic and solid elements, absence of detectable vascular flow, and a "spoke-like" appearance. Macrocalcification was observed only in adults. These features should sensitize physicians performing thyroid ultrasound to the possible presence of underlying DICER1 syndrome.

RFC5.3

Experience of thyroid surgery in children with intraoperative neuromonitoring

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Introduction: Thyroid surgery in children is associated with high risk of recurrent laryngeal nerves (RLN) damage. It is due to complex and variable anatomy, high bleeding which decreasing visualization and requiring instrumental hemostasis. Large goiters change of syntopy, metastatic process requires bigger aggression and volume of intervention. The risk of damage significantly increases during repeated operations due to the scar process. There is significant experience of intraoperative neuromonitoring in adult patients. Such studies in children are not sufficient, and recommendations are often automatic transferred from adult practice.

Aim: To evaluate the effectiveness of intraoperative neuromonitoring of the recurrent laryngeal nerves during thyroid surgery in children.

Materials and Methods: 33 children from seven to 17 years old were operated on: 32 with thyroid diseases and one with parathyroid carcinoma. Intraoperative neuromonitoring was performed for 32 children. During surgery, RLN were mapped by monopolar stimulating probe. Nerve conduction after mobilization was tested by bipolar stimulating probe. In all cases was control of the electrical conductivity from n. Vagus. All children underwent otolaryngology examination before and after the operation with an assessment of the vocal cords mobility.

Results: Stimulation level during nerve mapping in children should be lower (up to 1 mA) compared with adult patients (from 2 mA). This allows getting an answer to the impulse with more local stimulation. In two cases, the use of monopolar coagulation had a pronounced effect on equipment in the form of false answers. In 5 cases the signal was lost both through the recurrent laryngeal nerve as n. Vagus. In case of parathyroid carcinoma ipsilateral loss of signal led to a reduction of intervention volume to avoid bilateral paresis. Nerve damage level could be determined by stimulation on different sites. Characteristic, in all cases the nerve was not visually damaged. Otolaryngology examination confirmed partial unilateral paresis in all these cases. Clinically, paresis was not manifested by changes in voice. Significant positive dynamics to improve of the vocal cords mobility in injured site was noted after a course of phoniatric rehabilitation.

Conclusion: Intraoperative neuromonitoring in children does not reduce the number of paresis (15%). This allows to change the surgical tactics in time and more active way to conduct phoniatric rehabilitation. These circumstances, as well as the improvement of surgical techniques using neuromonitoring, give a hope for improving the results of surgical treatment of thyroid diseases in children.

RFC5.4

Thyroid dysfunction in patients following thymus transplantation in a tertiary centre: A 10-year experience

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Background: Thymus transplantation is undertaken for conditions associated with severe immunodeficiency. These comprise a number of genetic and syndromic associations including 22q deletion syndrome, CHARGE association, diabetic embryopathy, and other rarer conditions. Autoimmune thyroid dysfunctions (Hashimoto's thyroiditis and Graves' Disease) are described in the literature as the most common autoimmune disease after thymic transplant.

Objective: To determine the frequency and aetiology of thyroid dysfunction following thymus transplantation at a tertiary center.

Case Series: Total 33 patients (age 2 months-2 years, 20 male) from the UK and 13 European centres underwent thymus transplantation between 2009-2018. The underlying diagnoses included 22q11.2 (n=18, 1 with a phenotype only of 22q11.2), CHARGE association (n=10), diabetic embryopathy (n=2), FOXN1 mutation (n=2), and TBX1 mutation (n=1).

24 patients (72.2%) were assessed for thyroid status prior to transplant. Pre-transplant thyroid function test (TFT) abnormalities were found in 5 patients. Secondary hypothyroidism n=2 (Typical DiGeorge and *TBX1* mutation). Persistently raised TSH with normal FT4 n=1 (CHARGE). Transiently raised TSH with normal FT4 n=2.

Post-transplant TFT results were available for 16 patients (48.49%). Of these, 3 patients had normal thyroid function, and 3 had pre-existing thyroid dysfunction prior to transplant. 10 patients (62.5 %) developed post-thymic transplant thyroid dysfunction. Autoimmune thyroid disease (positive anti-TPO antibodies) were found in 5 patients (31.2 % of total cohort). Of these, 3 were found to have a raised TSH with Low FT4 at time and were commenced on levothyroxine treatment. T4 assay interference on post-mortem samples was confirmed in 1 patient, who had an undetectable T4. 1 patient has normal thyroid function to date with positive anti TPO antibodies. Transiently raised TSH (normalization within 6 months) was seen in 3 patients.

Thyroid dysfunction was observed as early as Day 8 post-transplant to 2-years post-transplant. The mean time to develop autoimmune thyroid disease was 1.2 years after transplant (7 month- 2 years).

Conclusion: This case series highlights the variability of thyroid dysfunction in patients undergoing thymus transplantation. This vulnerable cohort is at significant risk of thyroid dysfunction. Assay interference should be considered while analyzing TFT post-thymic transplant.

The lack of standardized evidence-based guidelines for the investigations and management of these patients has important implications for morbidity, mortality and healthcare costs.

RFC5.5

A novel mutation in the Thyroglobulin gene leading to Neonatal goiter and Congenital Hypothyroidism in an Eritrean infant

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Background: Congenital hypothyroidism is a common condition with reported incidence between 1/2000 – 1/4000 live births. In approximately 85% of cases this is sporadic due to a structural abnormality of the thyroid gland. Approximately 15% of cases are hereditary and secondary to thyroid dyshormonogenesis. Most of these are due to mutations in one of the genes involved in iodine transport or organification, mutations in the thyroglobulin gene or defects in iodothyrosine deiodinase. These conditions are usually transmitted in an autosomal recessive fashion and cause hypothyroidism of varying severity.

We present a case of an infant of Eritrean origin, presenting with congenital goiter, congenital hypothyroidism and a novel mutation identified in the thyroglobulin gene.

Case Report: An Eritrean woman presented at term with no antenatal follow-up.

Fetal ultrasound exam revealed a large mass in the neck and upper chest consisting of 2 lobes consistent with an enlarged thyroid gland.

A live female infant was delivered in good condition. Initial examination was notable for a large diffuse neck swelling and mild respiratory distress with no other abnormal examination findings.

Initial Thyroid Function: TSH 272.39 mIU/l (0.4-20) FT4 6.3 pmol/l (10-30) FT3 5.5 pmol/l (2.46-9.8)

Thyroglobulin 0.7 picg/l (0-55) Thyroglobulin antibody <20U/ml

Thyroid ultrasound demonstrated enlargement of both lobes of a hyperemic thyroid gland, with normal echogenicity. Thyroid technetium scan (^{99m}Tc) demonstrated a diffusely enlarged thyroid gland with diffusely increased uptake.

Due to the findings of neonatal goiter, primary hypothyroidism, low serum titer of thyroglobulin and increased uptake of technetium on nuclear scanning, a genetic defect in the thyroglobulin gene was suspected and genetic studies were undertaken.

Genetic Studies: Sequencing of the thyroglobulin gene revealed a homozygous donor splice site mutation at the exon 30-intron 31 boundary; c.5686+1delG. This is a novel rare mutation with no

homozygotes reported. It affects one of the invariant residues at the donor splice site. Other mutations at this site have been shown to be pathogenic. Along with the clinical phenotype this mutation is highly likely to be pathogenic.

Summary: We present an infant of Eritrean origin presenting with a congenital goiter, primary hypothyroidism, a low serum thyroglobulin and increased uptake on thyroid technetium scanning. Sequencing of the thyroglobulin gene revealed an as yet unreported change, highly likely to be pathogenic, as a donor splice site mutation with low allele frequency in an area in which other pathogenic mutations have been identified.

RFC5.6

Complex single nucleotide polymorphisms in SERPINA7 lead to TBG deficiency

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Objective: Thyroxine binding globulin (TBG) is the most important thyroid hormone transporter in humans and is encoded by the SERPINA7 gene located on chromosome Xq22.2. By analyzing the genes of TBG-deficient patients, we aim to find a new molecular basis for the possible etiology of the disease.

Design and Methods: 10 groups of subjects were enrolled in the pediatric department of the First Affiliated Hospital of Zhejiang University School of Medicine from 2016.1-2017.12 for the diagnosis of TBG deficiency. SERPINA7 gene was detected by PCR and whole-genome sequencing. Totally, six mutations were found, one was a deletion mutation and the other five were missense mutations. Analyzed the conserved and pathogenicity of these mutations using the online program UCSC Genome Brower, MutationTaster, and PolyPhen-2, and analyzed the three-dimensional structure of the variant proteins using Swiss-Model. Cloned the wild type and mutant cDNA into pcDNA3.1(+) plasmid vector, and then transfected the HEK-293T cells for 48h, measured TBG levels in cell culture medium by ELISA. 6 single mutations and 7 groups of complex mutations were analyzed to evaluate the effect on TBG secretion.

Results: Identified 10 patients who carried complex hemizygous mutation (c.271G>A/c.909G>T, c.275T>C/c.909G>T, c.631G>A/c.909G>T, c.880C>T/c.909G>T, c.927delC/c.909G>T, c.271G>A/c.631G>A/c.909G>T). 1 deletion mutation (c.927delC, p.I310Ffs10) and 4 singlenucleotidepolymorphism(SNP)(c.271G>A, p.E91K, c.631G>A, p.A211T, c.880C>T, p.R294C, c.909G>T, p.L303F), 1 possible pathogenic mutation (c.275T>C, p.I92T). One of the 10 patients carried a single hemizygous mutation c.909G>T, p.L303F; 3 patients carried a composite hemizygous mutation c.631G>A, p.A211T/c.909G>T, p.L303F; 2 cases carried c.275T>C, p.I92T/c.909G>T, p.L303F; the other 4 cases were c.271G>A, p.E91K/c.909G>T, p.L303F, c.880C>T, p.R294C/c.909G>T, p.L303F and c.909G>T, p.L303F/c.927delC, p.I310Ffs10. One case is a multiple complex hemizygous mutation c.271G>A, p.E91K/c.631G>A, p.A211T/c.909G>T, p.L303F. In vitro expression analysis showed that TBG secretion caused

by a single missense mutation was only slightly reduced or not decreased, while the composite mutation resulted in a significant decrease in TBG secretion, and the deletion mutation resulted in complete TBG deficiency. In addition, the more mutations carried, the greater the effect on TBG secretion.

Conclusion: We believe that the polymorphism of the SERPINA7 gene can be pathogenic, especially has multiple SNP sites at the same time, which could lead to decreased expression. The more SNPs are carried, the lower the TBG and the higher the likelihood of complete TBG.

Key words: TBG deficiency; SERPINA7 gene; mutation; SNP

Bone, Growth Plate and Mineral Metabolism Session 2

RFC6.1

EFTUD2 gene deficiency disturbs maturation of osteoblast and inhibits chondrocyte differentiation via activated p53 signaling

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Mandibulofacial dysostosis with microcephaly (MFDM) is characteristic of multiple skeletal anomalies comprising craniofacial anomalies/dysplasia, microcephaly, dysplastic ears, choanal atresia and short stature. Loss of function mutations of *EFTUD2* were previously reported in MFDM, however, the mechanism underlying *EFTUD2*-associated skeletal dysplasia remains unclear. Here, we identified a novel frameshift mutation of *EFTUD2* in a MFDM Chinese patient with craniofacial dysmorphism including ear canal structures and microcephaly, mild intellectual disability and developmental delay. We have generated a zebrafish model of *eftud2* deficiency and consistent phenotype of mandibular bone dysplasia and otolith loss were observed. We have also shown that *EFTUD2* deficiency significantly inhibited proliferation, differentiation and maturation in human calvarial osteoblasts (HCO) and articular chondrocytes (HC-a). RNA-Seq analysis uncovered activated TP53 signaling with increased phosphorylation of TP53

protein and upregulation of five *TP53* downstream target genes (*FAS*, *STEAP3*, *CASP3*, *P21* and *SESN1*) both in HCO and in *eftud2*-/- zebrafish. Additionally, inhibition of *p53* by morpholino significantly reduced the mortality of *eftud2*-/- larvae. Together, our results suggest that *EFTUD2* may participate in the maturation of osteoblast and is necessary for chondrocyte differentiation, possibly via activation of the TP53 signaling, and thereby, leading to skeletal anomalies in vertebrates.

RFC6.2

High levels of LIGHT/TNFSF14 in Prader-Willi syndrome

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Background: Low bone mineral density (BMD) has been found in up to 50% of adolescents and adults with Prader-Willi syndrome (PWS). High fracture risk has been described in adult PWS patients. However, the mechanism/s of low BMD in PWS have not been clarified. These patients also display high BMI-SDS that prompted us to evaluate the levels of LIGHT/TNFSF14, a cytokine involved in pathological bone remodeling and obesity.

Objective and Hypotheses: To evaluate the levels of LIGHT/TNFSF14 in PWS children and to correlate them with parameters of obesity and bone quality.

Method: Nineteen PWS children were enrolled (5M/14F, 11.35 ± 6.76) and LIGHT/TNFSF14 levels were measured in the sera. Bone status, lean mass and fat mass were assessed by DXA.

Results: Significant higher LIGHT/TNFSF14 levels were found in PWS patients than controls (426.73 ± 374.63 pg/ml vs 162.26 ± 72.47 pg/m, p<0.006). LIGHT/TNFSF14 levels significantly correlated with IGF-1 (r=-0.534 p<0.04), PTH (r=0.393 p<0.04), femoral Z-score (r=-0.437 p<0.04), lumbar-z-score (r=-0.711 p<0.01), lean mass % (r=-0.656 p<0.02), total fat (r=0.597 p<0.04), trunk fat % (r=0.638 p<0.03), left arm fat (r=0.779 p<0.002), right arm fat (r=0.697 p<0.01).

Conclusion: We demonstrated high serum levels of LIGHT/TNFSF14 in PWS children that correlated with both fat and bone mass. This cytokine could contribute to obesity and bone disease affecting PWS patients, therefore representing a good pharmacological target.

RFC6.3

Increased burden of common risk alleles in children with a significant fracture history

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Background: Fractures are common in children, but a significant fracture history, defined as low-trauma vertebral fractures or multiple long bone fractures, is rare. Children with such history and no osteogenesis imperfecta (OI) are often presumed to have another Mendelian disease. However, in adults, multiple common risk alleles of small effect influence risk of fracture. We tested if subjects with a significant childhood fracture history have an increased burden of common risk alleles.

Methods: We generated a polygenic risk score for quantitative ultrasound speed of sound, termed "gSOS", derived from common risk alleles in 341,449 UK Biobank participants. Low gSOS predicts adult osteoporotic fracture. We tested if two cohorts with a significant childhood fracture history and no OI had lower predicted gSOS. The Canadian cohort included 94 subjects with suspected Mendelian osteoporosis. Of them 26 had positive and 68 negative OI gene panel. The Finnish cohort included 59 individuals recruited due to a significant fracture history and 25 subjects referred for suspected Mendelian osteoporosis; 5 had positive OI gene panel. 11 individuals of non-European ancestry and individuals with OI, or who failed genotyping were excluded. We computed gSOS estimates in the two cohorts and compared their gSOS to that of a UK Biobank subset. We counted the individuals with significant fracture history and identified OI and compared them to those having gSOS below the mean in excess of what would be expected by chance alone.

Results: The average gSOS in the entire cohort (n= 133) was -0.70 (standard deviation [SD]: 0.46) and was lower than that in UK Biobank (n=80,027, average gSOS: -0.48 [SD:0.45], P= 4.2 x 10⁻⁷). The gSOS of those evaluated for Mendelian osteoporosis was lower than that of those with only significant fracture history (average gSOS osteoporosis subset (n=80): -0.83 (SD: 0.41) vs fracture-prone subset (n=53): -0.51 [SD: 0.47], P=9.8 x 10⁻⁵). Finally, among 101 individuals with fractures tested for Mendelian disease, 31 had a mutation in an OI-related gene, while there were 21 more subjects with a gSOS below the mean than would be expected by chance alone.

Conclusions: We provide evidence for a polygenic etiology of fractures in children with significant fracture history and no OI. This suggests that patients with clinically-apparent Mendelian disease referred to specialists might have a burden of common risk alleles which could influence their risk of fracture.

RFC6.4

Targeted Molecular Genetic Diagnosis by Next Generation Sequence Analysis Method and Investigation of Responsible Candidate Genes in Patients with Osteogenesis Imperfecta

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Introduction: The aim of this study was to investigate the molecular genetic etiology and to determine the relationship between genotype and phenotype with targeted next-generation sequence (NGS) analysis.

Method: Patients with a clinical diagnosis of OI were included in the study. Initially, mutations in COL1A1 and COL1A2 genes which are known to be most responsible for OI were investigated. In the second step, a targeted NGS panel (Illumina TruSight One) containing genes involved in collagen/bone synthesis was performed on the Illumina NextSeq550 platform in cases without mutations of COL1A1 and COL1A2. Pathogenicity of determined variants was determined according to ACMG criteria.

Results: Of the 42 patients (F/M:17/25), 13(31%) of the parents had consanguineous marriage and 21(50%) had a family history of affected individuals. The mean age at admission was 4.5±3.8 years, and the median body weight and height SDS was -1.3 (-6.8-1.2) and -2 (-7.6-0.8)SD. 18 of the patients (42.9%) were evaluated as type 1, 3(7.1%) as type 2, 15(35.7%) as type 3, and 6(14.3%) as type 4 clinically. While bone deformity was detected in 23(54.8%) of the cases, 22(52.4%) was independently mobile. Blue sclera was found in 27(64.3%) of the patients, scoliosis in 11(26.2%), dentinogenesis imperfecta in 6(14.3%) and hearing loss in 2(4.8%). Mutation in COL1A1 and COL1A2 gene was found in 20(47.6%), and in 3 patients (7.1%) respectively. One (2.3%) patient had a mutation in both genes. In 16 (38%) of the remaining 25 patients, 3 different gene (SERPINF1, FKBP10, and P3H1) mutations were found with targeted sequence analysis. 13 (39.3%) of the mutations detected in all investigated genes were not previously reported in the literature and were considered to be disease-specific according to in-silico analysis programs. In nine (21.4%) of the patients, a disease-related mutation was not found in a total of 15 genes, which were known to be associated with OI and were included in the panel list. Advanced genetic analyzes are ongoing in cases whom no mutation is found.

Conclusion: This study is a comprehensive research that shows the clinical and molecular characteristics of OI disease. Genetic etiology was found in 33 (78.5%) of 42 cases by targeted sequence analysis. In addition, 13 new mutations were assessed in OI genes which can be defined as significant contribution to the literature.

RFC6.5

Evaluating genotype-phenotype correlation using an *in vitro* mutagenesis model in bi-allelic mutations resulting in extreme hypophosphatasia clinical phenotypes

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Introduction: Hypophosphatasia (HPP) characterized by reduced mineralization results from mutations in the tissue non-specific alkaline phosphatase (*ALPL*) gene. HPP is clinically variable with extensive allelic heterogeneity in the *ALPL* gene. We report the findings of *in vitro* functional studies following site-directed mutagenesis in bi-allelic mutations causing extreme clinical phenotypes; severe perinatal and asymptomatic HPP.

Objectives: Elucidate genotype-phenotype correlation using *in vitro* functional studies and 3 dimensional (3D) ALP modelling.

Methods: Clinical, biochemical and radiological features were recorded in two subjects (S) with extreme HPP phenotypes: S1: Perinatal HPP with compound heterozygous mutations (c.110T>C; c.532T>C); S2: Asymptomatic with homozygous missense mutation (c.715G>T). S2's affected siblings (3 homozygous, 1 heterozygous) were also studied.

Plasmids created for mutants 1 c.110T>C (L37P), 2 c.532T>C (Y178H) and 3 c.715G>T(D239Y) using *in vitro* mutagenesis were transfected into human osteosarcoma (U₂OS) cells and compared to wild type (WT) and mock cDNA. ALP activity was measured using enzyme kinetics with p-nitrophenylphosphate. Mineral deposition was evaluated photometrically with Alizarin Red S staining after culture with beta-glycerophosphate. Western blot analysis was performed to identify the mature type protein expression (80 kDa). Mutations were located on a 3D ALP model.

Results:

Phenotype: S1 had extremely under-mineralized bones and pulmonary hypoplasia, typical of perinatal HPP. S2, diagnosed incidentally at 4 years, had normal growth, dentition and radiology similar to the siblings. All subjects had typical biochemical features of HPP (low ALP, high serum pyridoxal-5'-phosphate and urinary phosphoethanolamine) except heterozygous sibling (normal ALP).

Functional Assay: Mutants 1 and 2 demonstrated negligible ALP activity and mineralization (7.9% and 9.3% of WT, respectively). Mutant 3 demonstrated 50% ALP activity and 15.5% mineralization of WT. Western blot analysis detected mutants 1 and 2 as faint bands indicating reduced expression and mutant 3 as mature form protein (50% of WT expression). Mutant 1 was located near the Glycosylphosphatidylinositol anchor, 2 at the core structure and 3 at the periphery of the ALP protein structure.

Conclusion: Our findings expand the current knowledge of functional effect of individual mutations and the importance of their location in the ALP structure. c.715G>T homozygous mutation showed no clinical variability enabling phenotype prediction in offsprings and genetic counselling.

RFC6.6

Genetic aetiology predicts growth hormone (GH) treatment outcomes in children born small-for-gestational-age with persistent short stature (SGA-SS). Lessons from a single-centre cohort

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Background: SGA-SS, defined as birth weight and/or birth length below -2SD for gestational age and postnatal statural height below -2.5SD according to age- and sex-specific standards, is a heterogeneous condition reflecting exogenous (maternal, placental) or endogenous (foetal) inadequacies. Within the past two decades, a handful of genetic causes of SGA-SS have been elucidated. However, how each genetic aetiology impacts individual GH treatment outcomes awaits clarification.

Aim: To analyse treatment outcomes in genetically defined subgroups of SGA-SS children originating from a single-centre cohort.

Patients/Methods: A single-centre cohort consists of 445 SGA-SS children (221 females; Turner syndrome was excluded) aged 1.3-27.0 years at this evaluation (median 11.8). Of these, genetic aetiology was thus far elucidated in 60 children (33 females) - 24 carried a pathogenic variant of genes affecting the cartilage (ACAN in two, collagen genes in nine, and SHOX gene in 13), 19 had pathogenic genetic variants perturbing GH-IGF axis and signalling (GHSR [1], HGMA2 [3], OTX2 [1], STAT3 [1], IGFALS [1], IGF1R [2], Silver-Russell syndrome [SRS; 10]), and 17 had miscellaneous single-gene or chromosomal conditions.

We analysed (1) systemic response to GH administration expressed as delta-IGF-1_SDS prior to and while on treatment and (2) target tissue response expressed as delta-height_SDS on treatment.

Results: Whereas the systemic response to GH therapy was equivalent in children with undetermined aetiology of SGA-SS (delta-IGF-1_SDS following the first 3-6 months of GH: +1.50±0.10; mean±SEM) and the subcohorts with cartilage defects (+1.47±0.36) and perturbed GH-IGF axis (+1.42±0.46), the target tissue response clearly differed. The height gain following first two years of prepubertal GH therapy was higher in the subcohort with perturbed GH-IGF axis (delta-height SDS: +1.12±0.09) than in children with cartilage defects (delta-height SDS: +0.84±0.09; p=0.046), whereas children with undetermined aetiology had an intermediate two-year growth response (delta-height SDS: +0.96±0.04).

Conclusions: The best SGA-SS responders to GH therapy are apparently children with perturbed GH-IGF axis and signalling, including SRS children. The treatment response in children with defective growth cartilage (bearing either cartilaginous matrix or chondrocyte regulation defect) was rather modest. The change of IGF-1 following therapy is a poor predictor of growth outcome. Our results open an insight into treatment outcome prediction in SGA-SS, however their reproducibility may be limited due to small counts in individual subcohorts. Thus, analyses in larger cohorts of genetically defined SGA-SS children are warranted.

Diabetes and Insulin Session 2

RFC7.1

Accuracy of glucose sensor estimate of HbA1c in children with type 1 diabetes

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Introduction: Glucose sensor usage is increasing in the paediatric type 1 diabetes population. The sensor downloads can provide valuable information about glycaemic levels over a 90-day period and generate an estimated HbA1c based on the average glucose level.

Aim: We aimed to test whether the sensor-estimated HbA1c over 90 days was an accurate prediction of the measured HbA1c and whether its accuracy correlated with percentage sensor data captured.

Methods: Over a 12-week period, 90-day sensor downloads were collected from children with type 1 diabetes who were wearing a glucose sensor (Freestyle Libre or Dexcom G5) on the day they were due their 3-monthly HbA1c laboratory test. The Freestyle Libre handset was downloaded in clinic and the Dexcom G5 was accessed through Clarity online portal to generate the reports. Each family provided informed consent for their data to be used in the study. The HbA1c was measured by ion-exchange high-performance liquid chromatography (HPLC) from EDTA whole blood. The difference between the measured and calculated HbA1c was calculated (delta HbA1c).

Results: Twenty four children who were wearing glucose sensors had HbA1c tests during the study period (20 were wearing Freestyle Libre and 4 Dexcom G5). The mean laboratory HbA1c was 7.85% (SD 1.39, Range 5.8 to 12%). The mean predicted HbA1c was 7.66% (SD 1.52, Range 5.3 to 11.4%). The mean delta HbA1c was 0.18% (SD 0.58, Range -1.1 to +1.4%), with a tendency for the prediction to be lower than the measured HbA1c in 67% of cases. The mean delta HbA1c for the Freestyle Libre was 0.1% and for the Dexcom G5 0.7%. The estimated HbA1c was within 0.5% of the laboratory HbA1c 50% of the time and within 0.75% 79.2% of the time. Bland Altman Analysis confirmed there was no relationship between the level of HbA1c and the delta HbA1c, or between percentage sensor data captured and delta HbA1c.

Conclusions: There is a tendency for estimated HbA1c to be lower than the measured HbA1c but the mean difference is small. The delta HbA1c is significant in a few individuals but there was no correlation with lower sensor wear time or higher HbA1c. The sensor download provides a useful estimate of the HbA1c and the estimated HbA1c is within 0.75% of the measured HbA1c 79.2% of the time. With increasing sensor accuracy the estimated HbA1c may eventually replace the need for a 3-monthly HbA1c blood test.

RFC7.2

β -cell function and glucose effectiveness in the development of impaired fasting glucose in obese European children and adolescents

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Objectives: Impaired fasting glucose (IFG) is a risk factor for the development of type 2 diabetes in adults. In obese children and adolescents, IFG and impaired glucose tolerance constitute distinct prediabetic stages, which do not necessarily coexist. Pathophysiological mechanisms leading to IFG in children have not been fully elucidated. Available data from cohorts of obese adolescents living in the US suggest a concurrent worsening of insulin sensitivity and β -cell function. If these results can be applied to European populations is currently unknown.

Methods: Here we combine our method for mathematical modelling of insulin secretion and disposal from 3h, 8 sample OGTT data in children and adolescents (Vogt et al., Am J Physiol Endocrinol Metab. 311:E82-94, 2016) with a minimal model of glucose to estimate insulin sensitivity SI, β -cell responsiveness Phi, and insulin-independent glucose disposal (SG) in a population of n=284 (n=146 girls) obese children and adolescents (\bar{x} age 13.8 ± 3.0 years), \bar{x} BMI z-score 2.73 ± 0.75. A subpopulation of n=34 children underwent a follow-up OGTT (median time to follow-up 1.92 years).

Results: Of the total study population, n=12 subjects were diagnosed with IFG. After adjustment for age, IFG subjects were characterized by a 12% lower β -cell responsiveness Phi ($p<0.01$), higher insulin sensitivity SI (+15%, $p=0.05$), and significantly decreased glucose effectiveness SG (-19%, $p=0.04$) compared to NFG subjects. In the follow-up cohort, all n=34 patients were NFG at baseline, and n=4 progressed from NFG to IFG. At baseline, SI did not differ between 'progressors' and stable subjects, but Phi was higher (60.8 pmol/min per mg/dl vs. 38.2 pmol/min per mg/dl) and SG was decreased in progressors compared to stable subjects (adjusted for age, each $p<0.001$). Progression from NFG to IFG was associated with a significant decline in β -cell responsiveness (-14.5 pmol/min per mg/dl), moderately decreasing insulin sensitivity (-4.2%), and significant worsening of SG (-17.5%; all p-values for intra- and inter-group comparisons <0.04, adjusted for age), whereas all three parameters remained unchanged in stable subjects.

Conclusions: Impaired fasting glucose is a prediabetic stage characterized by a defect in β -cell function and significantly impaired glucose effectiveness in our large cohort of obese children and adolescents living in Middle Europe. Our data demonstrates for the first time, that in children and adolescents progression from NFG to IFG is driven by declining β -cell function and a marked collateral decrease in insulin-independent glucose disposal, ultimately leading to disruption of fasting glucose homeostasis.

RFC7.3

Osteopontin as an Early Urinary Marker of Diabetic Nephropathy in Adolescents with Type 1 Diabetes Mellitus

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Introduction: Patients with type 1 diabetes (T1D) have a higher rate of morbidity and mortality compared with the general population, which varies across countries. Diabetic nephropathy (DN) is a common and serious complication of T1D. Osteopontin (OPN) is a calcium binding phosphoprotein that is expressed in glomerular basement membrane. OPN can be a potential marker of vasculopathy and subclinical atherosclerosis and hence a predictor of DN in T1D patients. The aim of the study is to evaluate urinary OPN as an early marker for DN in children and adolescents with T1D.

Subjects and Methods: This cross-sectional study was carried out on 60 children and adolescent with T1D diagnosed more than 5 years, with age range (7-18 years), they were divided into two groups according to albumin creatinine ratio (ACR), normoalbuminuric: ACR < 30 mg/g (n=30); microalbuminuric: ACR 30-300 mg/g (n=30). Urinary OPN was measured in all T1D patients.

Results: The anthropometric and clinical data among the two patient groups showed no significant difference. Urinary OPN (ng/ml) was significantly higher in microalbuminuric than normoalbuminuric patients ($P<0.001$). There was significant positive correlation between urinary OPN (ng/ml) and ACR ($P <0.001$)

Conclusion: Longer duration of diabetes and poor glycemic control are associated with increased risk of developing DN. Urinary OPN can be a noninvasive early marker for DN.

RFC7.4

Handgrip Strength Correlates with Insulin Resistance and the Metabolic Syndrome in Children and Adolescents: Analysis of the Korean National Health and Nutrition Examination Survey 2014-2016

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Introduction: Reduced muscle strength is associated with increased cardiometabolic morbidity and mortality. Handgrip

strength (HGS) is an indicator of muscle strength and has been correlated with total muscle strength in children and adolescents. We aimed to evaluate the association between HGS and parameters of the metabolic syndrome and insulin resistance in children and adolescents.

Methods: A total of 2,242 children and adolescents (age 10-18) participated in the Korean National Health and Nutrition Examination Survey (KNHANES) between 2014 and 2016. Those 1,646 healthy children (884 males) with measurements of HGS, anthropometrics, and metabolic syndrome parameters were included. For analysis of insulin resistance, a subgroup of 555 children with fasting insulin levels were included. HGS was analyzed by the combined HGS (CHGS; the sum of the largest reading from each hand expressed in kilograms) and was further normalized for bodyweight (nCHGS).

Results: At a mean age of 14.4 ± 0.1 years, 198 (12.3%) participants were obese and 208 (12.9%) had abdominal obesity. The metabolic syndrome was present in 40 (2.4%) participants. The mean nCHGS was 0.95 ± 0.01 kg/kg bodyweight. There was an increasing trend for abdominal obesity, elevated fasting glucose, hypertension, hypertriglyceridemia and low HDL with decreasing quartiles of nCHGS (P for trend < 0.05 , for all). Presence of the metabolic syndrome was significantly increased with decreased nCHGS (P for trend < 0.05). Subgroup analysis of participants with insulin levels showed that nCHGS was significantly decreased in participants with increased insulin and HOMA-IR levels. The negative correlation of nCHGS with insulin ($\beta = -0.72$, $P < 0.001$) and HOMA-IR ($\beta = -0.71$, $P < 0.001$) remained significant after adjustment for sex, age, physical activity and sedentary time.

Conclusions: Normalized handgrip strength was significantly decreased in all parameters of the metabolic syndrome and insulin resistance. Normalized handgrip strength, a simple measure of muscular fitness, can be useful in predicting the presence of cardiometabolic risk factors in children and adolescents

RFC7.5

Dual diagnosis of type 1 diabetes and ADHD

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Background: Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood. Type 1 diabetes (T1DM) is the most common metabolic disease in children. The treatment of T1DM requires high executive functions

and requires very intensive treatment that could be an obstacle for patients with ADHD. Dual diagnosis of T1DM and ADHD might affect treatment, control and complications of T1DM. In order to prevent long-term complications we should target glycaemic control to HbA1c lower than 7% as well as low glucose variability. The aims of this study were to compare the following parameters between children with T1DM with or without ADHD: HbA1c, episodes of severe hypoglycaemia, diabetes ketoacidosis (DKA), quality of life (QOL), time in range and glucose variability parameters.

Methods: T1DM patients aged 6-18 years were recruited from 3 paediatric diabetes clinics. ADHD screening questionnaire was given to parents of T1DM patients without ADHD diagnosis. Patients with "suspected ADHD" were excluded from the study. All parents filled a Diabetes QOL questionnaire. Glycaemic data was downloaded from glucometers, pumps and CGMs. Other data, including HbA1c, hospitalisation, severe hypoglycaemia and DKA events were retrieved from the medical files.

Results: The study cohort comprised 111 patients with T1DM: 27 were diagnosed with ADHD (24%) and 84 without ADHD (Control group). Mean \pm SD age of the ADHD group and Control group was 14.6 \pm 2.8 and 12.6 \pm 3.3 years, respectively ($p=0.006$). Mean HbA1c was significantly higher in the ADHD group, 8.5 \pm 1.2 % vs. 7.8 \pm 1.0 % ($p=0.003$). There was no difference in QOL and in severe hypoglycaemia or DKA events between the groups. Sixty-two patients used CGM, 13 (21%) with ADHD. Time in range (TIR) (70-180 mg/dl) was significantly lower in the ADHD group, 49 \pm 17% vs. 59 \pm 15% ($p=0.05$). In a regression model for age the following parameters retrieved from CGMs were significantly higher in the ADHD group vs. the Control group: mean glucose ($p=0.024$), SD of glucose ($p=0.028$), TIR ($p=0.015$), percentage time above 180 mg/dl ($p=0.025$), percentage time above 240 mg/dl ($p=0.015$), and in glucose variability parameters: ADRR ($p=0.016$), HBGI ($p=0.009$), MAGE ($p=0.042$). There were no differences in percentage time below 70 mg/dl and below 55mg/dl.

Discussion: Coexistence of T1DM and ADHD during childhood leads to significantly higher HbA1c, TIR and glucose variability parameters compared to patients without ADHD. Healthcare providers should be aware of the difficulties of patients with T1DM and ADHD to get organised and to cope with the current intensive treatment of diabetes.

RFC7.6

Health-Related Quality of Life and Diabetes Control in Immigrant and Italian Children and Adolescents with Type 1 Diabetes and in their Parents

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Background/Objectives: Type 1 diabetes (T1D) is a chronic metabolic disease that requires daily and complex management for both patients and their caregivers, impairing the quality of life. Aim of this cross-sectional observational study was to determine whether metabolic control and health-related quality of life (HRQOL) of T1D subjects and their parents could be influenced by immigration status.

Methods: We enrolled 125 children and adolescents with T1D (12.4 \pm 3.55 years; males 53.6%; T1D duration 5.61 \pm 3.50 years) and their parents (102 mothers and 37 fathers). According to patients' maternal origin, the study population was categorized into Group A (immigrant) and Group B (Italian). The Italian translation of the PedsQL™ 3.0 Diabetes Module was used to evaluate the HRQOL. Information on presence of diabetic ketoacidosis (DKA) at T1D onset, insulin therapy (MDI/SAP), and glycosylated hemoglobin (HbA1c), were collected at the same time of the questionnaire.

Results: Group A, respect to Group B, had significantly higher frequency of DKA at T1D onset (55.0 vs. 22.3%; Chi-Square=13.1; $p<0.001$) and a significant lower use of SAP (5.0 vs. 22.3%; Chi-Square=5.86; $p=0.015$). HbA1c values were significantly higher in Group A respect to Group B (72.7 \pm 17.6 vs. 62.6 \pm 12.9 mmol/mol; $p<0.001$). Patients' HRQOL scores were significantly lower in Group A than in Group B in the following scales: "Diabetes self-symptoms" (57.9 \pm 14.6 vs. 66.9 \pm 12.8; $p=0.004$), "Treatment barriers" (68.1 \pm 23.6 vs. 82.9 \pm 13.0; $p=0.001$), and "Worry" (52.9 \pm 26.9 vs. 66.9 \pm 23.7; $p=0.009$). Mothers' HRQOL scores were significantly lower in Group A than in Group B in the following scales: "Diabetes self-symptoms" (56.7 \pm 18.1 vs. 65.8 \pm 15.7; $p=0.030$), "Treatment barriers" (55.9 \pm 19.8 vs. 71.3 \pm 19.7; $p<0.001$), "Treatment adherence" (71.2 \pm 18.1 vs. 80.6 \pm 11.2; $p=0.018$), "Communication" (58.9 \pm 31.4 vs. 75.9 \pm 23.3; $p=0.009$) scales, and total score (57.2 \pm 17.1 vs. 68.8 \pm 12.6; $p=0.011$). No differences were found in fathers' data. The multivariate regression model for child HRQOL scales identified the following significant predictive factors: MDI insulin therapy ($\beta=0.438$; $p=0.008$), Italian ethnicity ($\beta=0.018$; $p=0.004$), HbA1c ($\beta=-0.228$; $p=0.029$) for "Treatment barriers" scale; Italian ethnicity ($\beta=0.584$; $p=0.046$) for "Worry" scale.

Conclusions: Our results strongly suggest that immigrant status confers significant disadvantages in terms of T1D treatment, glycemic control, and HRQOL in children and adolescents with T1D. Moreover, parents' HRQOL data suggest that daily T1D management is usually supervised by mothers rather than fathers. Specific challenges and educational interventions should be considered in clinical care of T1D patients with distinct migration background.

Pituitary, Neuroendocrinology and Puberty Session 1

RFC8.1

Trade-off between Olfactory Bulb and Eyeball Volume in Precocious Puberty

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Context: Olfactory bulb (OB) and eyeball size change depending on age and puberty. There is well-established trade-off between sensory structures of brain such as eye and olfactory bulb.

Objective: The aim of this study is to analyze the potential reciprocal changes between OB and eyeball volumes (EV) in girls with precocious puberty (PP), as a sign of early pubertal onset.

Design: A total of 148 girls aged between 5-8 years (63 PP, 85 healthy) were included in the study. Exclusion criteria: Cases of anosmia/hyposmia, neurodegenerative disorder, refractive errors and trauma. The pituitary height (PH), EV and OB volume were measured on segmentation of magnetic resonance image slice using manual counteracting. The corrected measurements by body surface were used in all statistical analyzes.

Results: In girls with PP, the means of OB volume and pituitary height (PH) were larger (71.11 ± 20.64 ml) and higher (4.62 ± 1.18 mm), respectively, while mean of EVs was smaller (11.24 ± 2.62 cm 3) ($p=0.000$). Cut-off values were 62.27ml, 10.7cm 3 and 4.71mm for OB volume, EV and PH, respectively. While the negative correlations were found between OB volume-EV and EV-PH ($r_{63}=-0.224$, $p=0.001$ and $r_{63}=-0.116$, $p=0.001$, respectively), OB volume was positively correlated with PH ($r_{63}=0.578$, $p=0.001$).

Conclusion: The present study demonstrates that girls with PP have significantly larger OB volume, but smaller EV, and there is negative correlation between two structures. These results indicate that OB plays a more active role than previously thought on pubertal activity, and there is trade-off between anatomical dimensions of OB and eyeball in favor of OB in PP girls.

RFC8.2

Investigation of imprinting alterations in *MKRN3* and *DLK1* in a cohort of girls with central precocious puberty through specific DNA methylation analysis

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Background: Loss of imprinting has been implicated in the pathogenesis of several human diseases. Monogenic causes of central precocious puberty (CPP) were identified in families with loss-of-function mutations in two paternally expressed imprinted genes: Makorin zinc finger 3 (*MKRN3*) and Delta-like 1 homolog (*DLK1*). The role of imprinting defects in CPP has not been described so far.

Objective: To investigate the methylation status at primary differentially methylated regions (DMR) of *MKRN3* and *DLK1* in a cohort of CPP patients.

Patients and Methods: Fifty-six CPP girls (48 sporadic, 8 familial) were selected for analysis. They had normal hypothalamic-pituitary region MRI. Leukocyte DNA was obtained from all patients. *MKRN3* and *DLK1* pathogenic allelic variants were initially excluded by DNA sequencing analysis. Bisulfite treatment followed by Allele-Specific Methylated Multiplex Real-Time Quantitative PCR was performed with leukocyte DNA, analyzing separately the methylation index (MI) of *MKRN3*:TSS-DMR and *DLK1*/*MEG3*:IG-DMR for each patient. Results were compared with MI of 50 adult controls, 15 prepubertal controls girls and 18 pubertal controls girls with normal pubertal development.

Results: Mean age at puberty onset was 6.1 ± 1.9 yr for all CPP girls. Hypomethylation at *DLK1*/*MEG3*:IG-DMR was identified in two patients with sporadic CPP (patients I and II), confirming a molecular diagnosis of Temple syndrome. Interestingly, both girls had been firstly referred to pediatric endocrinology for presenting precocious menarche. During follow-up, other clinical findings were noticed: being born small for gestational age, prominent forehead, small hands/feet, overweight and hyperinsulinemia or early type 2 diabetes. SNP array was performed in patient I, identifying a partial uniparental disomy at chromosome 14 (upd(14)). On the other hand, patient II had normal CGH array and microsatellites analysis, excluding copy number variations and upd(14), and indicating a mechanism of epimutation. In the remaining patients, mean MI for *DLK1*/*MEG3*:IG-DMR was $49 \pm 1.5\%$. In all patients, mean MI for *MKRN3*:TSS-DMR was $49 \pm 5\%$. Besides that, as a group, there were no significant correlations between age at puberty onset and: 1) MI for *MKRN3*:TSS-DMR ($p=0.69$) and 2) MI for *DLK1*/*MEG3*:IG-DMR ($p=0.45$).

Conclusion: There were no leukocyte DNA methylation defects at *MKRN3* imprinting control region. *DLK1/MEG3*:IG-DMR hypomethylation was identified in two patients with CPP. Loss of effective imprinting of *DLK1* locus may be a mechanism involved in the etiology of CPP, and should be investigated in patients presenting additional findings of Temple syndrome.

RFC8.3

Central Precocious Puberty Caused by Novel Mutations in the Promoter and 5'-UTR region of the Imprinted *MKRN3* Gene

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Background: Central Precocious Puberty (CPP) is clinically defined by the development of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys. To date, mutations in the coding region of *KISS1*, *KISS1R*, *DLK1* and *MKRN3* genes have been reported as causative for CPP. This study investigated the presence of causative mutations in both the promoter and the 5'-UTR regions of the *MKRN3* gene.

Methods: Sanger DNA sequencing was used for screening the proximal promoter and 5'-UTR region of the *MKRN3* gene in a group of 73 index girls with CPP. Mutations identified were cloned in luciferase reporter gene vectors and transiently transfected in GN11 cells in order to check for changes in the activity of the *MKRN3* promoter. GN11 cells were previously checked for *Mkrn3* expression using lentivirus mediated knock-down. *In silico* analysis was implemented for the detection of changes in the mRNA secondary structure of the mutated *MKRN3* 5'-UTR.

Results: Three novel heterozygous mutations (-166, -865, -886 nt upstream to the transcription start site) located in the proximal promoter region of the *MKRN3* gene were identified in six non-related girls with CPP. Four of these girls shared the -865 mutation, one the -166 and another one the -886. A 5'-UTR (+13 nt downstream to the transcription start site) novel mutation was also identified in a girl with similar clinical phenotype. Gene reporter assay evaluated the identified promoter mutations and demonstrated a significant reduction of *MKRN3* promoter activity in transfected GN11 cells. *In silico* analysis for the mutated 5'-UTR predicted a significant change of the mRNA secondary structure. The minimum free energy (MFE) of the mutated 5'-UTR was higher when compared to the corresponding wild-type indicating less stable RNA secondary structure.

Conclusion: Our findings demonstrated novel genetic alterations in the promoter and 5'-UTR regulatory regions of the *MKRN3* gene. These changes add to another region to check for the etiology of CPP.

RFC8.4

Evaluation of puberty in patients with Noonan syndrome and mutations in the RAS/MAPK genes

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Background: Noonan syndrome (NS) is a rare genetic disease characterized by facial dysmorphism, short stature, heart defects, chest deformities, and variable developmental delay/learning disabilities. Almost 80% of patients have a mutation in the genes encoding components of the RAS/MAPK pathway. Puberty was described as delayed in NS patients, but few studies are focusing on this subject and genotype-phenotype correlations so far.

Objective: To evaluate puberty in patients clinically and molecularly diagnosed with NS.

Methods: This study was a retrospective analysis 84 NS patients (37 females) with mutations in the RAS/MAPK pathway genes (56 PTPN11, 5 RAF1, 5 SOS1/2, 4 KRAS, 3 BRAF, 3 RIT1, 3 LZTR1, 2 SHOC2, 1 NRAS, 2 MAP2K1/2). Genotype-phenotype correlations were analyzed between patients with PTPN11 mutations (n=56) and patients with mutations in other NS related genes (n=28).

Results: Age at puberty onset and menarche in girls was 11.8 ± 1.9 years and 14.5 ± 1.9 years (n=17), respectively. Eight out of 37 girls (22%) had delayed puberty. Age at puberty onset was 12.8 ± 2.1 years in boys, and 16 out of 47 boys had delayed puberty (34%). Frequency of delayed puberty was similar in boys and girls. Patients with delayed puberty were shorter than patients with normal puberty (height-SDS of -3.9 ± 1.0 vs. -2.0 ± 1.0 , respectively; $p < 0.001$). BMI-SDS was lower in patients with delayed puberty in comparison with those with normal puberty (-0.6 ± 1.1 vs. -1.7 ± 1.4 ; $p < 0.001$). Age at menarche was higher in delayed puberty girls (16.0 ± 1.7 vs. 13.8 ± 1.7 ; $p = 0.017$). Height-SDS ($p < 0.001$) and BMI-SDS ($p = 0.05$) can negatively predict age at puberty onset in a multiple linear regression model ($R^2 = 0.40$). No difference was observed concerning the frequency of delayed puberty, puberty onset, age at menarche, height-SDS, and BMI-SDS between patients with or without mutations in the *PTPN11* gene.

Conclusions: Delayed puberty was observed in 29% of NS patients. Patients with delayed puberty were shorter and thinner than patients with normal puberty resembling constitutional delay of growth and puberty. Prospective studies are required to further investigate the link between metabolism and puberty in NS patients.

RFC8.5

CHD7 mutations in patients with anosmic or normosmic idiopathic hypogonadotropic hypogonadism

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Background: Mutations in *CHD7* cause a rare multi-organ system disorder, CHARGE syndrome (CS). Genital hypoplasia has been described in 60-80% of reported cases because of idiopathic hypogonadotropic hypogonadism (IHH), which is a result of inadequate GnRH secretion in the hypothalamus. Correspondingly, IHH and anosmia are expected in cases with *CHD7* mutation. However, due to the phenotypic spectrum of *CHD7*, mutations have also been reported in IHH patients without typical CS features. Therefore, we aimed to identify *CHD7* "uncertain significance" RSVs to expand the known spectrum in IHH patients who could not include in any CS classification.

Methods: RSVs in *CHD7* were screened in anosmic and normosmic IHH patients without CS classification or criteria. Determined RSVs were evaluated according to ACMG/AMP standards. gnomAD was used to identify variants with MAF <0.01%. DANN score and pathogenicity were determined using VarSome and InterVar. "Pathogenic", "likely pathogenic" and "uncertain significance" classification criteria were evaluated and others excluded.

Results: Eight missense "uncertain significance" alterations (p.Arg459Cys, p.Gly1260Ser, p.Ala2733Thr, p.Asn785Ser, p.Arg886Trp, p.Ser559Leu, p.Asp2390Glu, and p.Pro515Ala) and one nonsense "pathogenic" variant (p.Gln61Ter) detected in *CHD7* from nine unrelated IHH patients without CS criteria.

Seven of nine patients had also IHH related gene variants including *SEMA3E*, *WDR11*, *OTUD4*, *FGF17*, *FGFR1*, *PCSK1*, *RAB3GAP2*, *AXL*, and *PCSK1* in the heterozygous state.

Conclusion: Based on our data, RSVs of uncertain significance in *CHD7* according to ACMG/AMP criteria may be associated with anosmic and normosmic IHH. The discovery of the increasing number of RSVs in *CHD7* showed that this gene is becoming progressively prominent in the IHH. The RSVs ratio, which may be causal, in IHH-related genes has been found quite high in our cohort (77.7%). As a result of focused researches, it is known that novel genes are added to the list of genes responsible for oligogenic inheritance both anosmic and normosmic IHH. For these and similar reasons, we think that it is important not to ignore the missense variants in genes known to be usually disease-causing truncating mechanisms, such as *CHD7*. These findings confirm that *CHD7* variants can lead to a broad spectrum of phenotypes, and suggest that the *CHD7* product is required for the GnRH migration. Accordingly, patients with IHH phenotype should be examined for possible *CHD7* mutations, even if they do not have CS characteristics. In addition, major and minor criteria of CHARGE syndrome should be further investigated if *CHD7* mutations are detected to allow for more optimal patient management.

RFC8.6

Growth, pubertal course and long-term outcome of 46,XY boys born with atypical genitalia and low birthweight

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Introduction: Boys born small for gestational age (SGA) often have undermasculinized genitalia. Little is known about the pubertal development and gonadal function on a longer-term in this specific group of males.

Aims: To determine the (pubertal) development and long-term urological and endocrine outcome of undermasculinized boys born SGA compared to undervirilized boys born appropriate for gestational age (AGA).

Methods: Clinical data were retrieved from the I-DSD Registry on boys with non-specific 46, XY DSD who were aged ≥2 years at the time of the study. Statistical analyses included: Pearson Chi-Square, Fisher's Exact, unpaired Student t-test, Mann-Whitney U test and Shapiro-Wilk test, as appropriate.

Results: Data of 179 cases (115 SGA, 64 AGA) from twelve centers were included. At 2 years of age, 31/104 SGA boys (29.8%) had incomplete or absent catch-up growth. Sufficient catch-up growth was even less likely in cases with comorbidities, birth length or weight ≤-3SD or preterm birth ($p=0.019$, 0.017 and 0.030 , respectively). Eight SGA cases had received growth hormone therapy. At last assessment, both SD-scores for height and weight were lower in SGA boys (both $p<0.001$) at a median age of 8.0 (SGA) and 7.7 years (AGA). Delayed neuromotor development was present in 19.6% and 1.9% of SGA and AGA boys, respectively ($p=0.001$).

The number of reinterventions for hypospadias repair was similar in both groups (1 (2); p=0.836). At last assessment, nearly all cases had an external masculinization score of 12/12, with residual hypospadias being the most frequent cause of lower scores in both groups.

Postnatal or childhood treatment to stimulate penile growth was reported to have a good clinical effect in 38/42 (90.5%) SGA and 14/15 (93.3%) AGA cases. LH levels during minipuberty were higher in SGA boys, with lower peak testosterone levels post stimulation (p=0.037 and 0.040 respectively). The majority of cases had a spontaneous onset and uneventful course of puberty. At the end of puberty, no difference in sex hormone levels was observed between SGA and AGA boys.

Conclusions: About one-third of boys with non-specific XY DSD who have SGA show insufficient catch-up growth. The urological outcome and effect of treatments to increase penile size was similar between SGA and AGA cases. Our data suggest a dysfunction of infantile Leydig cells in SGA boys, which does not seem to persist in adult-type Leydig cells. Alternatively, alteration of the hypothalamic-pituitary-gonadal axis during infancy may underlie the hormonal changes found in SGA boys.

Fetal, Neonatal Endocrinology and Metabolism (to Include Hypoglycaemia)

RFC9.1

Targeted next-generation sequencing for congenital hypothyroidism with positive neonatal TSH screening results

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Background and Objective: Congenital hypothyroidism (CH) is mostly detected with neonatal newborn screening (NBS). CH is the most common neonatal endocrine disorder with an incidence of 1:2,000-1:4,000. However the molecular etiology is still poorly understood, considering pathogenic variations in candidate genes have been found only in 10-20 % of CH. We performed mutations screening of causative genes through a systematic Next Generation Sequencing (NGS) analysis in CH cases with positive NBS results.

Methods: We performed the genetic analysis of causative 59 genes using NGS in 168 CH cases (53 dyshormonogenesis, 32 dysgenesis, 83 not evaluated). Pathogenicity of novel mutations was assessed in silico.

Results: We identified 12.5 % (21/168) and 5.4 % (9/168) with seemingly monogenic defects and oligogenic defects, respectively. Monogenic defects (21 cases) involved *DUOX2* (12), *TSHR* (5), *TG* (2), and *PAX8* (2). Oligogenic defects (9 cases) had two mutations in two different genes among *DUOX2*, *TG*, *TSHR*, *SLC16A2*, *GLIS3*, *TPO*, *SECISBP2*, *DUOXA1*, and *SLC26A4*.

Discussion: This study identified 12.5 % of monogenic defects in NBS-positive CH, which is similar result as previously reported. In addition, we found 5.4 % in CH patients having oligogenic defects. The role of oligogenicity in etiology of CH remains unclear, however frequent occurrence of several mutations in two or more candidate genes suggest the contribution of oligogenic variants. The systematic NGS analysis is useful in determining an underlying molecular etiology of CH.

RFC9.2

Age-specific reference values for plasma FT4 and TSH concentrations in healthy, term neonates at day three to seven, and 13 to 15 of life

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Background: Congenital hypothyroidism (CH) is a common and preventable cause of mental retardation in children, and is detected using dried blood spots in many neonatal screening programs. Upon suspicion of CH, plasma free thyroxine (FT4) and thyroid stimulating hormone (TSH) concentrations are measured. CH can be of thyroidal or central origin (CH-T and CH-C, respectively). While CH-T diagnosis is based on an elevated plasma TSH in combination with a low FT4, CH-C diagnosis is based solely on a low plasma FT4.

Currently, reliable neonatal reference intervals (RIs) for plasma FT4 and TSH are lacking. Age-specific neonatal RIs would greatly improve the diagnostic process for CH, especially for CH-C.

Objectives: To establish neonatal RIs for plasma FT4 and TSH concentrations in healthy, term neonates during the Dutch neonatal screening at day 3-7 (t=1) and at day 13-15 (t=2; day of birth is day 0). The current study was particularly designed to provide a reliable FT4 lower limit to facilitate the diagnosis CH-C. In the Netherlands, children with an abnormal screening result suggestive for CH-C are referred for pediatric consultation on average on day 14; time point for measurement t=2 was chosen accordingly.

Methods: Venous blood collection (heparin plasma) was performed in 120 healthy neonates at two time points. If plasma was missing for one time point, another participant was recruited for replacement (total number of participants >120). Here, we report our first 200 measurements.

FT4 and TSH concentrations were measured using an electrochemiluminescence immunoassay (Cobas, Roche Diagnostics, Switzerland; adult RI for FT4 12-22 pmol/L, TSH 0.5-5.0 mU/L). RIs were calculated with MedCalc for Windows (version 18.5, Belgium). If data were not normally distributed, the non-parametric percentile method was used.

Results: From 122 participants (53% female) ≥1 measurement was available. FT4 concentrations were normally distributed at both time points, while TSH concentrations were positively skewed. 95% RIs for FT4 were 20.1-37.5 pmol/L (day 3-7, n=104) and 15.0-26.9 pmol/L (day 13-15, n=96). 95% RIs for TSH were 0.8-8.4 mU/L (day 3-7) and 1.3-8.2 mU/L (day 13-15).

Conclusion: In this study, neonatal RIs for plasma FT4 and TSH were determined using the Cobas (Roche) immunoassay. Preliminary results indicate a FT4 lower limit of 20.1 pmol/L during the first week of life, and 15 pmol/L at the age of two weeks. This is considerably higher than the assay's lower limit of the adult RI for FT4.

RFC9.3

Neonatal screening for congenital hypothyroidism: analysis of a large coorte of affected patients (1987-2017) and relationship with perfluoroalkylated substances (pfas) in north-eastern italy

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Background: Recent studies have analyzed the influence of perfluoroalkylated substances – PFAS (in particular PFOS and PFOA) on people and thyroid. Children are primaly affected by these pollutants. On the other side variation of incidence of congenital hypothyroidism (CH) has been shown in recent years by different studies. We sought to determine whether the incidence of CH in north-eastern Italy has changed in relation to some endocrine disruptors and their potential effect on maternal and new-born health.

Methods: We analyzed data from the regional neonatal screening program for CH during the period 1987-2017 (more than 500 newborn with CH). We included all children having TSH values above the threshold and for whom diagnosis of CH was confirmed. We evaluated personal, biological and health data about both the mothers and the children. Environmental monitoring data about PFAS were provided by Arpav.

Results: The incidence of CH increased in North-eastern Italy during the past years, as the percentage of ectopic glands, furthermore there's an area with an increased number of cases, partially comparable to the area polluted by PFAS. Considering other aspects of pregnancies (about both mother and child), this study showed an higher rate of prematurity compared to general population (22% vs 7%) according to other studies conducted in Italy, and also an higher number of multiple pregnancies among mothers of CH children.

Conclusions: The raised incidence could partially be due to lowering cut-off but there's also a real increase of this condition in the population. The area with an increased number of cases is partially comparable to the area polluted by PFAS and more investigations are ongoing to establish the potential correlation. Some aspects of pregnancy show different percentages of CH compared to general population (multiple pregnancies, pre-term births and caesarean sections).

RFC9.4

Correlation between Genotype and Phenotype characteristics in Children with Congenital Hyperinsulinism (CHI) in a specialist centre

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Introduction and Aim: Congenital hyperinsulinism (CHI) is the most common cause of hypoglycaemia in early infancy and represents a heterogeneous disorder with respect to clinical presentation, histology and genetics. The aim of our study is to review correlation between genotype and phenotypic characteristics of children with CHI.

Methods: Retrospective review of CHI patients with positive genetics during the last 8 years in a specialist referral centre.

Results: Total of 71 children have so far been identified with positive genetic mutation (40 males). The majority had KATP channel (ABCC8/KCNJ11) mutation (n=55). 15 had compound heterozygous/homozygous KATP channel mutation. 30 had paternal and 10 maternal inherited KATP mutation. The rest were 9 HNF4a, 4 PMM2, 2 GLUD1 and 1 GCK mutation respectively. The median age of presentation with hypoglycaemia was 0-2 days in all mutations except GLUD1 (259.5 days). The median birthweight was significantly higher in children with KATP channel mutations than in GLUD1 and GCK. Diazoxide responsiveness was seen in 4 (26.7%) compound heterozygous KATP, 7 (23.3%) paternal inherited and 7 (70%) maternal inherited KATP channel mutation. 9 (88.9%) with HNF4a, 2 (100%) with GLUD1 and 1 (25%) with PMM2 showed complete response to diazoxide. Partial response to diazoxide was noted in 2 (13.3%) compound heterozygous, 3 (10%) paternal inherited and 1 (10%) with maternal inherited KATP channel mutation respectively. 3 (75%) with PMM2 mutation had good response to Nifedipine when used in conjunction with Diazoxide. 12 children with KATP channel mutation were managed on octreotide, sirolimus and Lanreotide. Natural remission was seen in 1 compound KATP (1.56 years), 5 (18.5%) in paternal KATP (median age 2.19 years), 5 (50%) in maternal KATP (median age 0.33 years) and 1 in HNF4a (0.66 years) mutation respectively. 21 patients (29.6%) underwent pancreatectomy (16 partial pancreatectomy for focal CHI and 5 subtotal pancreatectomy for diffuse form of CHI).

Conclusion: There is no significant difference noted in age of presentation amongst all except GLUD1 mutation which presents much later in life. Most children with KATP channel mutation require frequent feeds with multiple medications to manage severe form of CHI. Knowledge of genotype might help to determine pharmacotherapy. The odds of being fully responsive to diazoxide was greater in patients with maternal KATP channel than in homozygous, compound heterozygous and paternal inherited KATP channel mutation respectively.

RFC9.5

Spectrum of Neuro-developmental disorders in Children with Congenital Hyperinsulinism due to activating mutations in GLUD1

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Background & Objective: Hyperinsulinism-Hyperammonaemia (HI/HA) syndrome is the second most common type of congenital hyperinsulinism (CHI) in outbred populations. HI/HA is caused by an activating mutation in the *GLUD1* gene which encodes the intra-mitochondrial enzyme glutamate dehydrogenase (GDH).

The aim of this study was to determine the clinical presentation, treatment and risk factors of neuro-developmental disorders in children with HI/HA syndrome due to activating *GLUD1* mutations.

Method: Retrospective review of patients *GLUD1* CHI mutation treated at two specialist centers in the UK and Russia over a 15-year period. Statistical analyses included Mann-Whitney U test and Fisher exact p to assess the significance of different risk factors for neuro-developmental disorders.

Results: We identified 24 cases with *GLUD1* mutations (11 males). Median age of presentation was 23 weeks (12 hours-72 weeks). De novo mutation was confirmed in 12 (50%) cases. In 8 (30%) of them, the inheritance could not be established due to unavailability of parental samples. Hypoglycaemic seizures were the presenting feature in 23 (95.8%) cases. However, one patient presented with screaming at the age of 8 months. 23 cases responded to diazoxide and protein restriction whilst one underwent partial pancreatectomy due to uncontrolled hypoglycaemia on octreotide (as diazoxide unavailable).

In total, 16 cases (66.7%) developed a neuro-developmental manifestation. Epilepsy (n=9/24, 37.5%), learning difficulties (n=8/24, 33.3%) and speech delay (n=8/24, 33.3%) were the most common neurological manifestation followed by motor delay (n=7/24, 29.1%), abnormal movement (n=6/24, 25%) and vision problems (n=4/24, 16.7%). Median age of presentation for epilepsy was 42 weeks. In terms of seizures, generalized tonic-clonic

seizures were the most common (n=4/9, 44.4%) followed by absence seizures (n=3/9, 33.3%). Abnormal electroencephalogram (EEG) and brain magnetic resonance imaging (MRI) was found in 5/9 (55.6%) and 4/9 (44.4%) respectively.

Mutations in exons 11 and 12 of *GLUD1* gene (in charge of communication between adjacent GDH subunits) seems to be significant risk factor for epilepsy ($p=0.045$). Early age of presentation for CHI ($p=0.027$) was more likely to cause neurological disorder, while gestational age ($p=0.79$), birth weight ($p=0.85$), asphyxia ($p=0.10$) and ammonia level ($p=0.63$) do not seem to be associated with long-term neurodevelopmental disorders.

Conclusion: HI/HA syndrome is associated with wide spectrum of neurological disorders. Epilepsy, learning difficulties and speech delay are the most common neurological manifestation. These neurological manifestations seem to be more frequent in cases with mutations of GTP-binding site in *GLUD1* gene in our cohort.

RFC9.6

Extra Uterine Growth Restriction (EUGR) in very low birth weight infants: Growth recovery and neurodevelopment by the corrected age of 2 years old

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Background: Extra Uterine Growth Restriction (EUGR) represents a serious comorbidity in infants born very low birth weight (VLBW). In fact, failure in postnatal growth and malnutrition at vulnerable ages can interfere with growth recovery and neurodevelopment at older ages.

Hypothesis: Aim of the study was to assess whether and how the postnatal early growth patterns of VLBW may affect later growth, spontaneous motility at three months of corrected age (CA) and neurodevelopment at 2 years CA.

Study Design: Retrospective single-centre study of 547 infants (255M) born VLBW between 2005 and 2015. Each participant underwent: a) anthropometric assessments of weight (W), length (L) and head circumference (HC) at birth, at discharge from the NICU and at 2 years CA; b) Evaluation of Fidgety movements (F) at three months CA; c) Neurodevelopmental assessment at 2 years CA through the Griffith Mental Development Scales.

Results: From the overall population, growth percentiles at discharge were significantly lower than at birth (L $p<0.01$; W $p<0.01$; HC $p<0.01$). Longitudinal data showed a significant growth restriction between birth (AGA for W:73%; AGA for L:73.2%) and discharge (AGA for W:36%; AGA for L:31.2%). Gestational age, duration of hospitalisation, bronchopulmonary dysplasia and intra ventricular haemorrhage were found to be predictive factors for EUGR at discharge. At 2 years CA, SGA at discharge but not at birth, showed significantly lower stature compared to the AGA ones ($p:0.04$).

Significant correlation was found between F and L ($p=0.04$; $r=0.12$) and HC ($p<0.02$; $r=0.2$) at discharge, but not at birth. Moreover, a significant difference was found between F and locomotor outcome at two years CA ($p<0.01$). W and L at discharge, but not at birth, were significantly related to worse locomotor outcome at two years of CA (respectively, $p=0.03$, $r=0.14$; $p=0.01$, $r=0.18$). In particular, who was found SGA at discharge, both for W and/or L, had the worse motor outcome compared to the AGA ones (respectively, $p=0.04$ and $p=0.01$).

Conclusions: VLBW growth measurements at discharge, but not at birth, are related to poorer growth and neurodevelopment at later ages, especially in children who become SGA. Lower scores in locomotor assessment at two years CA have been observed in infants with anomalies of F, suggesting how spontaneous motility could predict later neurodevelopmental outcomes. Our findings highlight the necessity of a close clinical follow-up of growth patterns during preterm hospitalization aiming to decrease the incidence of EUGR.

Sex Differentiation, Gonads and Gynaecology or Sex Endocrinology

RFC10.1

Contemporary surgical approach in CAH 46XX – Results from the I-DSD/I-CAH Registries

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Introduction: Congenital adrenal hyperplasia (CAH) is the most common genetic condition in the spectrum of differences of sex development (DSD). Surgery in DSD is a controversial topic and there is no consensus if to perform surgery, how to perform surgery, and when to perform surgery. The current study was designed to evaluate the current practice in CAH related surgical practice in girls.

Patients and Methods: All cases that had been classified in the I-DSD and I-CAH registries as 46XX CAH born prior to 2017 were identified (555 participants in 41 centres, born 1953-2016). Centres were approached to obtain additional information in each eligible case on factors that influenced the option of performing surgery, timing and type of surgery. 330 participants were suitable for analysis.

Results: 208 (63%) presented within the first month of life; 306 (93%) had 21-hydroxylase deficiency. 326 (99%) cases were raised as girls after birth. At latest assessment, 329 (99.6%) cases had a female sex assignment. Genital surgery has been performed in 251 (76%). Clitoral surgery been performed in 231 (92%), vaginal surgery in 204 (81%) and a combination of clitoral and vaginal surgery had been performed in 186 (74%). Of the 251 who had surgery, 18 (7%) had vaginal but no clitoral surgery whilst 42 (17%) had clitoral but no vaginal surgery. Mean age at first surgery was 2.5 years (0-15), with clitoral surgery and vaginal surgery at 2.6 years (range) and 3.2 years (range), respectively. In a logistic regression model it could be shown that there was a negative trend for surgery over time. Moreover, there was a significant trend towards surgery before 24 months of life over time. However, there were significant geographic differences in the probability/incidence of

genital surgery: Europe 64%, Asia 97%, South America 89%. The Chicago Consensus Statement on DSD (comparison of data before and after 2006) did not have any significant influence on the timing or probability of surgery. Last but not least, age at first assessment showed to have a mild negative but non-significant effect on the probability of surgery.

Discussion: This is the largest international study to analyse the current surgical approach towards CAH. There are geographic and sociocultural differences. There is a trend towards avoiding/postponing surgery, especially in Europe. Moreover, there is a significant trend towards surgery before 24 months of life.

Five genes upregulated in the HIR group encode epigenetic modifiers, including CALM1, which is known to positively regulate the calcium-activated potassium channel activity of KCNH2. Curative GnRH treatment up-regulated 12 and downregulated 26 genes, indicating that testosterone is involved in their transcriptional regulation.

Conclusion: Defective mini-puberty induces differential expression of several genes important for cardiomyopathy and cardiac channelopathies. GnRH treatment upregulates several genes whose loss of function is implicated in SIDS indicating that testosterone may be involved as an etiological factor. As a consequence, careful cardiologic surveillance of HIR cryptorchid boys is warranted.

RFC10.2

Cryptorchid boys with abrogated mini-puberty display differentially expressed genes involved in sudden infant death syndrome

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Background: The long QT syndrome is the most frequent a well-established causative factor, among cardiac channelopathies, for the sudden infant death syndrome (SIDS). It accounts for approximately 12% of the cases. The non-transcriptional regulation of slowly activating delayed rectifier K+ currents and suppression of L-type Ca²⁺ currents by testosterone is a regulatory mechanism of cardiac repolarization that potentially contributes to the control of QTc intervals. SIDS has been described in patients with septo-optic dysplasia, Leopard syndrome (both have cryptorchidism in common) and mutations in TSPYL (leading to deficient T secretion). We hypothesize that impaired testosterone secretion during mini-puberty may increase the SIDS risk in cryptorchid boys by altering the expression of gene relevant for this syndrome.

Patients and Methods: 1. 15 boys with isolated cryptorchidism were selected and classified seven as Ad- (lack of Ad spermatogonia, abrogated mini-puberty, High Infertility Risk (HIR)) and eight as Ad+ (Ad spermatogonia present, intact mini-puberty, Low Infertility Risk (LIR)). During orchidopexy for bilateral cryptorchidism, biopsies are obtained for histology and RNA-Sequence analysis. 2. Seven HIR patients are randomized for treatment either with surgery followed by GnRH treatment or surgery alone. Randomization of patients to be treated or to remain untreated was completely unbiased by any parameter other than undescended testes. Among eight biopsies, four were taken before (testis 1) and four were taken after six months of GnRH treatment. They were compared to six samples, three of each were taken before (testis 2) and after six months of surgery alone, respectively.

Results: We analyzed 66 genes known to be implicated in SIDS. 82% (54/66) of these genes showed no differences in their mRNA levels between HIR vs LIR. Seven genes that were less expressed in the group of cryptorchid boys with defective mini-puberty are implicated in sick sinus syndrome development. Among them, CACNA1C and HCN4 positively responded to GnRH treatment.

RFC10.3

Level of Uncertainty in Diagnostic Evaluation of Boys With XY Disorders of Sex Development (DSD)

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Introduction: The degree of consistency between the findings from next generation sequencing (NGS) and detailed endocrine assessment is unclear in boys with XY DSD.

Objectives: Examine the range of endocrine and molecular genetic variation in boys undergoing evaluation for XYDSD.

Methods: Boys with XYDSD who were evaluated in Glasgow from 2016 to 2018 were included. Sequence variants were classified according to ACMG guidelines; Class 3 variants of uncertain clinical significance that were not reported clinically were divided into 3A and 3B, depending on the level of consistency of the phenotype with the genetic findings.

Results: 115 boys with median age of 0.9 yrs (range, 0.00,16.93) and median external masculinization score (EMS) of 8 (2,12) were identified. Endocrine assessment revealed an abnormality in 29 (25%) boys with a median EMS of 8.5 (2,11). The range of endocrine abnormalities consisted of disorder of gonadal development (DGD) in 19 (17%), LH-deficiency (LHD) in 8 (7%) and disorder of androgen synthesis (DAS) in 2 (2%). In the remaining 85 (75%) boys with non-specific DSD (NS-DSD), the median EMS was 8 (2,12). Of the 65 boys who had molecular genetic analysis by a combination of methods, variants were found in 8/55 (15%) by Sanger sequencing of seven genes and 16/40 (40%) by NGS of fifty-six genes. Of the 16 boys who had NGS-variants with a median EMS of 6.5 (2,12), 4 had Class 5, 1 had Class 4, 3 had a combination of Class 5/3A/3B, 5/3A and 5/3B, 5 had Class 3A only and 3 had Class 3A/3B combination. These included ANOS1, AR, CHD7, DHC7, FGF8, GATA4, HSD3B2, HSD17B3, MAMLD1, NR5A1, POR, PROK2, WDR11. Median EMS in boys with Class 5 and Class

4 variants was 5 (2,9) and 3 (3), respectively. Of 7 boys with Class 5 variants, 5 had normal and 2 had abnormal endocrine tests. One boy with Class 4 variant in *ANOS1* also had normal endocrine tests. Median EMS in 8 boys with Class 3A variants was 8.8 (2,12), of whom 5 had normal endocrine tests. There were 3 boys (NS-DSD,2; DGD,1) with a median EMS of 8.5 (7,10.5) who had Class 3B variants in *FGFR1*, *CYP11B1* or *RSPO1*.

Conclusions: Although the use of NGS increases the likelihood of a pathological variant, the extent of harmony with phenotypic features including endocrinology is variable. The clinical significance of Class 3 variants needs further research and there is a need to pool results from similar parallel activities worldwide.

RFC10.4

qPCR screening for Xp21.2 copy number variations in patients with elusive aetiology of 46,XY DSD

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Duplications of the dosage sensitive sex locus Xp21.2 have been associated with 46,XY gonadal dysgenesis (GD) for nearly 25 years. In the past, duplications have always included the *NR0B1* (nuclear receptor subfamily 0 group B, member 1, also known as DAX1) gene, a known antagonist of SF1 (Steroidogenic Factor 1) dependent SOX9 (SRY Box 9) activation and the GD was attributed to its “double gene dose”. However, recent findings have questioned the necessity of *NR0B1* to be included in the duplications and identified upstream copy number variations (CNVs) associated with 46,XY GD.

A real-time qPCR (quantitative PCR) routine for identifying CNVs at the Xp21.2 locus was established and validated using samples with known Xp21.2 duplications including and excluding *NR0B1* identified by chromosomal microarray analysis (CMA).

The qPCR was then used to screen 93 patients with elusive genetic cause of 46,XY disorders/differences of sex development (DSD). This revealed two previously unidentified duplications and one unidentified triplication of *NR0B1*. The number of published cases of non-syndromic *NR0B1* duplications associated with 46,XY GD is in the single digits and it remains a very rare diagnosis. Thus, Xp21.2 duplications are potentially underdiagnosed as cause of 46,XY DSD. The qPCR approach offers a short turnaround time at low consumable costs for identifying these patients. The CNVs could then be confirmed by other methods such as multiplex ligation mediated probe amplification, CMA and studied in more detail, including their point of insertion through whole genome sequencing.

RFC10.5

Variants in *NWD1* gene leading to different degrees of gonadal dysgenesis

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Introduction: Mammalian sex development is directly dependent on gonadal determination. Whole exome sequencing in patients with differences of sex development (DSD) allows the discovery of new factors involved in human sex development. One of these factors is *NWD1* (NACHT and WD repeat domain containing 1) a cytosolic protein that seems to play a role in modulating androgen receptor signaling. We identified variants in the *NWD1* gene in six undervirilized XY patients and in two XX patients. The phenotype of one of the patients with XX karyotype is described here.

Case Report: A 15-year-old female adolescent with normal stature presented with delayed puberty (B1), primary amenorrhea and retardation of bone maturation (bone age was 11 years according to Greulich & Pyle). She had normal body proportions. Lab work showed hypergonadotropic hypogonadism (LH 33.6 U/L, reference range: 1.1-3.8 U/L; FSH 106 U/L, reference range: 1.4-4.2 U/L) and unmeasurable estradiol. Testosterone was elevated (1.2 nmol/L, range: 0.2-0.6 nmol/L), ovarian autoantibodies were negative. The external genitalia were female, the uterus was present and the ovaries were very small without follicles at ultrasound. Due to the elevated testosterone value, diagnostic laparoscopy was carried out and ovaries were histologically assessed. The histological workup revealed streak gonads on both sides. The repeated elevated testosterone values are therefore most likely derived from precursors of adrenal origin. The patient was initially put under estrogen replacement therapy leading to normal pubertal development and further growth. Under combined estrogen/progesterone therapy regular menses occurred.

Whole exome sequencing revealed a mutation in *NWD1* gene. The patient's variant (c.350delA (Het)) leads to a frameshift and a premature stop codon (p.Asn117ThrTer11). 3D structure analysis shows that over 90% of the protein is lost leading most likely to either degradation or production of a shorter non-functional protein. This mutation is therefore likely to be associated with the clinical presentation of the patient.

Conclusion: The variant in *NWD1* gene is likely to be responsible for our patient's phenotype. Accordingly, 3D structure analysis showed that the mutation in this gene most likely leads to either degradation or inactivation of the protein. Another 7 patients with 46,XY and 46,XX DSD carry pathogenic variants in *NWD1*, suggesting that this gene might be part of the gonadal determination cascade in both sexes.

RFC10.6**A mutation in the nucleoporin-107 gene causes aberrant Dpp/BMP signalling and XX gonadal dysgenesis**

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Background: Though the genes and signalling pathways involved in sexual development have only been partially elucidated, it is known that their disruption can result in disorders of sexual development (DSD). XX ovarian dysgenesis (XX-OD) is a rare, genetically heterogeneous disorder characterized by underdeveloped and dysfunctional ovaries. We previously identified a novel missense mutation in Nucleoporin107 (Nup107, c.1339G>A, p.D447N), an essential component of the nuclear pore complex, as the cause of XX-OD in a consanguineous family.

Methods: The Nup107 mutation (D364N) was modelled in *Drosophila*, a powerful genetic tool sharing gene orthologues and fundamental pathways with humans, specifically in gonadogenesis. The structural integrity and presence of both adult mutant ovaries and the earlier-stage larval gonad were assessed using dissection. Differential gene expression between mutant and wild-type larval gonads was measured using genome-wide RNA-Seq followed by qRT-PCR. Immunohistochemistry was used to characterize cellular and signalling effects of the Nup107 mutation on both adult and larval stage ovaries.

Results: The Nup107 mutant flies directly mirrored the human phenotype of ovarian dysgenesis, where 40% of female transgenic flies possessed under- or non-developed ovaries. In contrast, the larval gonads were fully present, signifying that the underlying defects causing the condition occur following the larval gonad formation. The RNA-Seq studies revealed candidate genes with differential gonadal expression resulting from the Nup107 mutation, most of which possess human orthologs, including genes such as the serine protease scarface and ECM protein collagen type IVa1. Several of the candidates were found to be related to the Dpp/BMP signalling pathway. Antibody staining revealed both excess primordial germ cells (PGCs) in the larval gonad and high numbers of germline stem cells (GSCs) in the adult ovary phenotypes resembling that of Dpp/BMP overactivation and suggesting problematic germ cell differentiation.

Conclusion: The transcriptomic and cellular analyses strongly suggest that ovarian failure resulting from Nup107 mutation is mediated through the BMP pathway. This concept has implications for clinical evaluation as the human BMP signalling pathway and specifically BMP15 and BMP receptor BmprIB have been implicated in subfertility, and have been shown to be essential for female reproductive function. Testing of this pathway may be indicated in clinical cases of XX-DSD and premature ovarian failure.

Pituitary, Neuroendocrinology and Puberty Session 2

RFC11.1**National United Kingdom evidence- and consensus-based guidelines for the investigation, treatment and long-term follow-up of paediatric craniopharyngioma**

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Aims: Although rare, craniopharyngiomas are the commonest suprasellar tumour in childhood. Despite high overall survival, children and young people <19 years with craniopharyngiomas are at risk of multiple relapses and long-term tumour- and treatment-related neuroendocrine, cognitive and visual morbidity. A recent international survey highlighted the considerable variation in management strategies employed for these tumours, and the lack of any evidence- and/ or consensus-based guidelines. We sought to provide, for the first time, a national standard for best practice based on currently available evidence for the assessment, treatment and follow-up of paediatric craniopharyngiomas under the auspices of the Royal College of Paediatrics & Child Health (RCPCH), UK Children's Cancer & Leukaemia Group (CCLG) and the British Society for Paediatric Endocrinology & Diabetes (BSPED).

Methods: Clinical questions were formulated based on a PICO (Population, Intervention, Comparison, Outcome) format

by a multidisciplinary Guideline Development Group. Systematic searches were conducted via the Ovid MEDLINE (1946–February 2017) and Cochrane Library (2016, Issue 12) databases, identifying 2023 separate research articles. Publications underwent a three-tier filtering process and 300 were reviewed using the GRADE approach. Where recommendations could not be made, a two-stage international Delphi consensus process was conducted. The guideline was developed using AGREE II criteria.

Results: 44 clinical questions were identified, leading to 35 recommendations largely based on low to very low quality evidence. 30 further recommendations achieved >70% agreement via the Delphi consensus process. Important highlights include the recommendation that craniopharyngiomas are managed in tertiary paediatric centres with sufficient neuro-oncology, neurosurgery, endocrinology, radiology, pathology and neuropsychology multidisciplinary experience. At diagnosis, tumours should be graded using the “Paris” grading system (Puget *et al.*, J Neurosurg 2007; 106(Suppl 1):3–12) and subsequent surgical treatment tailored to avoid hypothalamic damage, with adjuvant upfront radiotherapy being offered where tumour resection is incomplete. Detailed recommendations on the neuroendocrine, ophthalmological and psychological pre-treatment assessment of patients and long-term follow-up of survivors are also made, with a review on the safety of growth hormone replacement therapy in this cohort.

Conclusions: These guidelines provide the first evidence- and consensus-based national recommendations for the management of paediatric craniopharyngioma, and highlight the need for further research in areas such as the efficacy of proton beam therapy, radiosurgery and intracystic therapies in children, and the management of late effects such as hypothalamic obesity. Through their implementation, we hope to achieve better consistency in the quality of care of such patients and improve long-term quality of survival.

RFC11.2

Prevalence and predicting factors of endocrine dysfunction in children with NF1 and optic gliomas

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Introduction: Up to 20% of children with neurofibromatosis type 1 (NF1) develops low-grade optic pathway gliomas (OPGs) that can result in neuroendocrinopathy.

The aim of the study was to identify prognostic factors for developing neuroendocrinopathies in patients with NF1 and OPGs before any treatment.

Methods: Records of 117 children with NF1 and OPGs followed at 4 Italian centers between 1997–2016 were retrospectively reviewed. We studied those endocrinopathies occurring before radiation therapy, chemo-therapy or surgery. OPGs were classified according to the modified Dodge classification (MDC).

Results: The NF1 median age at diagnosis was 1.8 years (range 0.1–12.8) and at diagnosis of OPGs was 4.2 years (range 0.4–13.7). Median follow-up was 9 years (range 0.2–35).

109/117(93.1%) OPGs were MDC1, 73/117(62.3%) MDC2, and 53/117(45.2%) MDC3/4. The chiasm was involved in 73(62%) tumors, hypothalamus in 37(32%).

Endocrine disorders were identified in 35(29.9%) children. Median age at diagnosis of endocrinopathies was 7.8 years (range 1.4–12.9 years). Among patients with endocrine disorders, the proportion of patients who later underwent any treatment for OPGs (both chemotherapy and/or surgery) was higher than in those without endocrine disorders (65.8% vs 24.4%; p=0.0001).

Considering the entire population the cumulative proportion of patients free from endocrine disease at 10 years of follow-up was 65.9%. Endocrine free survival declined up to 8 years post OPGs diagnosis. Hypothalamic involvement was the stronger single independent predictor of endocrine disorders (HR:7.48(95%CI:3.5–15.85), p<0.0001). Another independent predictor was age at OPGs diagnosis < 5 years (HR:2.51(1.09–5.8), p=0.03). Central precocious puberty (CPP) was diagnosed in 25 (14 males) children (71.4%) (median age 8 years; range:3.5–10.5), followed by GHD in 4(11.4%) children (median age 9.4 years; range 8.4–11.5),

diencephalic syndrome in 4(11.4%) children (median age 4.6 years; range 1.4-5.8), growth hormone hypersecretion in 2(5.7%) children (median age 4 years; range 3.9-4.1).

Conclusions: Endocrine disorders are common in patients with NF1 and OPGs independently from any treatment. Hypothalamic involvement and young (<5 years) age at OPGs diagnosis were predictors of endocrine disorders. CPP was the most prevalent diagnosis while GHD was not common as previously described. A high index of suspicion for very rare endocrine disorders such as diencephalic syndrome and growth hormone hypersecretion is important in these patients, especially in younger ones.

Patients with OPGs and endocrine disorders, because of the frequent hypothalamic involvement, need a particularly careful follow-up as they are more at risk to need treatment, both CT and surgery.

RFC11.3

Polycystic Ovarian Syndrome in Adolescents: Utilising Discovery Proteomics and the Search for to Identify Novel Non-Invasive Biomarkers

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Background: Polycystic ovarian syndrome (PCOS) is common, affecting up to one-fifth of females. PCOS is associated with significant comorbidity including metabolic dysfunction, pro-inflammation and mood disorders. Despite this, it is poorly understood, and diagnosis and management remain challenging in adolescents. Proteomics enables the better understanding of disease mechanisms and facilitates the identification of novel biomarkers.

Objectives: To describe the clinical phenotype of PCOS in adolescents and undertake discovery proteomic urine profiling using ultra-performance liquid chromatography-mass spectrometry (UPLC-MS/MS) to identify novel non-invasive biomarkers of PCOS.

Method: This prospective longitudinal study recruited females meeting NIH diagnostic criteria for PCOS from adolescent endocrinology and gynaecology clinics. The following were measured at baseline and annual follow-up: pituitary, adrenal and ovarian hormones, metabolic markers including an oral glucose tolerance test, psychological, menstrual, pubertal and anthropometric parameters, and pelvic ultrasounds. We have undertaken UPLC-MS/MS and developed new methods for discovery proteomic profiling of urine in an attempt to identify new disease mechanisms, drug targets and potential biomarkers.

Results: We have recruited 40 participants (median age 15.0 years, range 12.5-18.3), with two-thirds completing annual follow-up to date. Clinical signs at presentation included acne (89%), hirsutism (78%) and acanthosis nigricans (49%). Two-thirds of

participants had depressive or anxiety symptoms yet only one-third were known to mental health services. Metabolic dysfunction was common at baseline; overweight/obesity (86%), elevated body fat (88%) and dyslipidaemia (35%). These parameters did not alter significantly at follow-up. Insulin resistance was almost universal at baseline and follow-up (91%). Impaired glucose metabolism was common but improved from baseline (29%) to follow-up (10%; $p=0.11$). Over two-thirds of participants had an elevated anti-Müllerian hormone, three-quarters had an elevated free androgen index. Elevated inflammatory markers (CRP/ESR) were present in 40% participants. Only three participants had definitive ultrasonographic evidence of PCOS. Interventions included lifestyle advice (27%), combined oral contraceptive pill (COCP) ± anti-androgen (16%), metformin (30%) or metformin + COCP ± anti-androgen (27%).

Conclusion and Future Directions: We have demonstrated that adolescents with PCOS are at high risk of metabolic dysfunction, inflammation and mental health disorders. As such, early diagnosis and intervention are imperative. However, current diagnostic and surveillance methods are suboptimal. We describe the use of urinary proteomics to study metabolic pathways affected in PCOS and the potential identification of novel non-invasive biomarkers. Subsequently, we will use this hypothesis-generating data-set to create a non-invasive and clinically translatable assay to aid diagnosis and stratify management of this common adolescent condition.

RFC11.4

Increased adrenal and testicular androgen concentrations before puberty and in early puberty correlate to adult height outcomes in males with Silver-Russell syndrome

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Background: In a previous study, we reported that adult height (AH) outcomes in growth hormone treated males with Silver-Russell syndrome (SRS) were negatively correlated with estradiol concentrations before start of puberty and in early puberty. Whether elevated estradiol concentrations originated from adrenal or testicular androgens is unclear. We aimed to describe androgen secretion patterns and investigate correlations between androgen concentrations and AH outcomes in this group of patients.

Methods: In a retrospective longitudinal single-center study 13 males with SRS and normal timing of adrenarche and pubertal onset were followed from 6 years of age until AH. Subjects were retrospectively divided into two groups: eight subjects with AH >1 standard deviation score (SDS) below the midparental height (MPH) were defined as nonresponders

(NRs), and five subjects with AH \leq 1 SDS below the MPH were defined as responders (Rs). Yearly, blood samples drawn in the morning, were stored at -80°C after separation and auxology and pubertal development were recorded. Dehydroepiandrosterone-sulfate (DHEAS) and androstenedione (A_4) were determined by liquid chromatography-tandem mass spectrometry, testosterone (T) and dihydrotestosterone (DHT) were determined by gas chromatography-tandem mass spectrometry. Correlations between androgens at different ages and AH outcomes were calculated using Spearman's nonparametric rank correlation. A P-value < 0.05 was considered significant.

Results: Several boys had elevated androgen concentrations prepubertally and in early pubertal stages compared to reference intervals. Before puberty, at testis volumes of 1-2 mL, seven NRs and two Rs had elevated concentrations of DHEAS, and eight NRs and three Rs had elevated A_4 concentrations. Moreover, two NRs had elevated T concentrations, and one NR had elevated DHT. In early puberty, at a testis volume of 3-6 mL, two NRs had elevated DHEAS concentrations, and four NRs and two Rs had elevated A_4 concentrations, whereas five NRs and one R had elevated concentrations of T and DHT.

AH outcomes correlated negatively to DHEAS at 8 ($r=-0.72$, $P=0.006$), 10 ($r=-0.79$, $P=0.001$) and 12 years ($r=-0.72$, $P=0.006$), T at 10 ($r=-0.94$, $P=0.000$), 12 ($r=-0.70$, $P=0.008$) and 14 years ($r=-0.64$, $P=0.018$) as well as DHT at 10 ($r=-0.62$, $P=0.025$) and 12 years ($r=-0.57$, $P=0.041$). No correlations with A_4 were found at any age.

Conclusions: Several boys had elevated androgen concentrations both prepubertally and in early puberty. Androgen concentrations before start of puberty and during early puberty correlated negatively to AH outcome in males with SRS. Both adrenal and testicular androgen secretion seem to contribute to elevated serum androgen concentrations.

Objective: To evaluate IGF-1 serum levels and growth before and after 12 months of leptin replacement therapy in patients with congenital leptin deficiency (CLD).

Patients and Methods: This case-series contains n=9 patients (6 males) with CLD due to defective production (n=5) or bioinactive leptin (n=4). We retrospectively analysed data regarding age, height-SDS, BMI-SDS, IGF-1-SDS, IGFBP3-SDS, IGF-1/IGFBP3 ratio-SDS at the beginning (T0), after 6 months (T6) and after 12 months (T12) of leptin replacement therapy.

Results: At baseline, mean age was 8.2 ± 5.4 yrs (range: 0.9-14.8 yrs), mean BMI-SDS was $+4.1 \pm 1.4$ (range: 2.3-6.0) and IGF-1-SDS as well as IGF-1/IGFBP3 ratio-SDS were negative in all patients (IGF-1-SDS $T_0: -1.16 \pm 0.83$, IGF-1/IGFBP3 ratio-SDS $T_0: -1.10 \pm 0.80$). Mean IGFBP3-SDS was 0.17 ± 1.36 . Leptin replacement resulted in a reduction of BMI-SDS of 1.40 ± 0.81 after 12 months. During leptin replacement therapy, IGF1-SDS increased from $T_0: -1.16 \pm 0.83$ to $T_6: -0.22 \pm 1.81$ and $T_{12}: +0.26 \pm 1.26$. We also observed an increase in IGFBP3-SDS and in IGF-1/IGFBP3 ratio-SDS ($\Delta_{T_0-T_{12}}\text{IGFBP3-SDS} = +0.67 \pm 0.95$, $\Delta_{T_0-T_{12}}\text{IGF-1/IGFBP3 ratio-SDS} = +1.16 \pm 1.81$). Mean change in height-SDS under leptin replacement therapy was not significant; however, when we looked at the individual data, we observed that all children younger than 12 yrs (n=5) showed a positive change (0.12-0.64).

Conclusions: Most studies show that obese children have normal or increased IGF-1 levels, and it is known that IGF-1 levels decrease under caloric restriction (Hawkes and Grimbberg, *Pediatr Endocrinol Rev*. 2015;13(2):499-511). Interestingly, we found that IGF-1 serum levels in severely obese CLD children were low at baseline and increased during metreleptin substitution despite reduced caloric intake. We also observed an acceleration of growth in children <12yo. Our findings support the hypothesis that leptin, as a signal of the energy status, promotes IGF-1 production and growth.

RFC11.5

IGF-1 serum concentrations and growth in children with congenital leptin deficiency (CLD) before and after replacement therapy with metreleptin

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Background: Leptin, primarily secreted by adipocytes, is a pivotal signal of the body's energy status and exhibits pleiotropic effects. Homozygous mutations in the leptin gene which result in defective synthesis, release or bioactivity, cause intense hyperphagia and early-onset severe obesity, along with multiple metabolic, hormonal, and immunological abnormalities. In vitro and animal model studies suggest that leptin plays a role in linear growth. So far, this has not been fully investigated in humans.

RFC11.6

Final height reduction in transgender adolescent girls: a case series

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Background: Transgirls (female-identifying adolescents assigned male at birth) can be treated with GnRH (gonadotropin releasing hormone analogs) followed by the addition of estrogens.

Recently in a small cohort of 25 transgirls their average final height was reported to be +1.9 SDS (standard deviation score) calculated for adult Dutch females.

High dosage estrogens can be used to stimulate bone maturation, thereby reducing final height. There are no reports on the effect of this treatment on final height in transgirls.

We present 11 cases of adolescent transgirls treated with high dose estrogens. Data on various approaches – limited duration of GnRH monotherapy, dosage and duration of estrogen therapy- and its efficacy on finale height are described.

Case Series: At the start of GnRHa therapy mean height was 169.2 (± 6.4) cm and the mean target height 186.4 (± 4.8) cm. During GnRHa monotherapy until the start of estrogen therapy the mean predicted final height increased from 189.4 (± 4.2) cm to 191.0 (± 4.4) cm. According to protocol estrogen therapy was started at 5 µg 17-beta estradiol/kg and increased with 5 µg/kg every 6 months. The high dosage estrogen scheme was either 6 mg 17-beta estradiol (case 2 to 11) or 200 µg ethinyl estradiol (EE) once daily (case 1). Height reduction was calculated by the difference between final height and the predicted final height. The mean predicted final height at start of estrogen therapy was 193.2 cm (+3.6 SDS for Dutch females), the mean final height was 188.9 cm (+2.9 SDS for adult Dutch females) which means an average final height reduction of 4.3 cm (-0.7 SDS). In 10 of 11 cases, final height was reduced. In 6 of those 11 cases estrogen therapy were started prior to the age of 16. In case number 8, estrogens were started initially in low dosage which led to an increase of predicted final height.

Conclusion: Final height reduction in transgirls using high dosage estrogens can be achieved. However, final height of these transgirls was still above the normal range of biological girls. Further height reduction is feasible but may require adjustment of protocol. First, estrogens should be started at an earlier age. Second, the dosage of growth inhibiting effect of 17 beta estradiol should be increased or alternatively the synthetic estrogens should be used. Awareness of an increased risk of venous thromboembolic events by using synthetic estrogens is required and should be explored further.

Design: Prospective experimental study using fluorescent *in situ* hybridization (FISH) of single ovarian cortical cells from young females with classic TS (45,X; n=5) or mosaic TS (45,X/46,XX; n=5). FISH signals were evaluated in stromal cells, oocytes and their corresponding granulosa cells, and compared to the karyotype of lymphocytes, buccal cells and urine cells of the same patient.

Methods: Intact ovaries from 10 females with TS (aged 2-18 years) were obtained by unilateral ovariectomy for fertility preservation purposes after informed consent was given. One fragment per patient was digested with a mix of proteases/DNase to obtain a cell suspension containing intact follicles and stromal cells. Stromal cells and primordial/primary follicles were transferred to coated microscope slides and prepared for FISH with chromosome X and chromosome 18 (control) specific centromere probes.

Results: In patients with 45,X karyotype in lymphocytes, buccal cells and urine cells, all ovarian stromal cells were 45,X and no follicles were found. In mosaic TS patients, the level of mosaicism of the ovarian stromal cells was very different from that observed in lymphocytes, buccal cells and urine cells. Analysis of follicles of these TS patients revealed that granulosa cells also display mosaicism that was different from the other cell types. Furthermore, individual follicles from the same ovary may have very different levels of mosaicism in their granulosa cells. While most oocytes of TS patients were found to have a 46,XX karyotype, we identified 4 oocytes in two patients with reduced X-chromosome content. Interestingly, some 46,XX oocytes were surrounded exclusively by 45,X granulosa cells.

Growth and Syndromes (to Include Turner Syndrome)

RFC12.1

Karyotyping of oocytes, granulosa cells and stromal cells in the ovarian tissue from patients with Turner syndrome: a pilot study

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Summary Answer: Most primordial/primary oocytes were found to have a 46,XX karyotype. Chromosome patterns of the ovarian cells were different from that observed in other tissues.

Background: TS is a chromosomal condition associated with partial or complete absence of one of the two X-chromosomes. Females with TS have a limited reproductive lifespan due to an accelerated loss of germ cells. It has been hypothesized that viable oocytes arise from 46,XX germ cells and that 45,X0 germ cells are eliminated. However, primordial follicles have been found in females with an 45,X karyotype. It is currently unknown if the karyotype found in lymphocytes, buccal cells or urine cells is representative for the karyotype in ovarian cells. Furthermore, it is unknown if oocytes in these patients have a normal karyotype.

RFC12.2

Treatment with growth hormone increases Klotho concentration in patients with Turner syndrome

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Background: Short stature, increased adiposity and insulin resistance are conditions frequently observed in patients with Turner syndrome (TS). Many hormones are involved in the pathogenesis of the condition but therapeutic options we can offer to the patients are still scant. Each newly discovered peptide give us hope. Klotho play a very important role in the regulation of the human body metabolism and was not investigated in patients with TS so far.

Objective and Hypotheses: The objective of the study was to investigate the concentration of Klotho protein and the response to the treatment with rHGH in patients with TS.

The study group consisted of 28 patients with TS diagnosed in one pediatric tertiary center. Their mean age was 7.6 years (range 3.2-16.1 years). The patients were diagnosed by karyotyping. Conventional G-banding and fluorescence *in situ* hybridization on peripheral blood cultures confirmed numerical or structural abnormalities of X chromosome or mosaicism. X chromosome

monosomy was established in 14 patients (50%). Because of short stature the patients were treated with rHGH given subcutaneously once a day at bedtime, in a dose 0.05 mg/kg/day. The dose of rHGH was adjusted to body weight every 3 months. The mean period of treatment was 1.4 yr (range 0.4-3.6 yr). No other medication including estrogen replacement therapy was conducted during the study. Patients with coexisting endocrine diseases were excluded. Prior to and following the rHGH treatment anthropometric data were recorded as well as biochemical parameters were measured: Klotho, OGTT, insulin, lipids, IGF-1, and IGFBP-3.

Results: The treatment with rHGH caused a significant rise in Klotho level ($1386,3 \pm 663,9$ vs $3421,5 \pm 1320,0$, mean \pm SD, $p = 0,000$). The increase of IGF-1 SDS at the end of observation was also significant (-1.68 ± 0.49 vs 0.36 ± 1.42 , mean \pm SD, $p = 0,000$). The rHGH treatment influenced insulin resistance revealed by increased HOMA values (0.82 ± 0.56 vs 1.46 ± 1.6 , $p = 0.02$). The correlation between Klotho and IGF-1 SDS levels was not significant neither before nor on the treatment. Klotho correlated with IGFBP3 level before rHGH treatment but not on rGH therapy. Klotho also correlated negatively with HDL cholesterol ($r=-0,6$) and positively with triglycerides ($r=0,4$) before rHGH applying.

Conclusions: Result of the study showed an increase in Klotho level following rHGH application. This effect is not mediated by IGF-1. Klotho can be used as a marker of the response to the treatment with rHGH

Method: To detect genetic causes of these patients, we first performed methylation analysis using pyrosequencing for the *PLA-GL1*-, *PEG1/MEST*-, *PEG10*-, *H19*-, *Kv*-, *DLK1-MEG3* intergenic-, *MEG3*-, *SNRPN*-, *ZNF597*-, and *GNAS A/B*-DMRs. For patients with abnormal methylation of these DMRs, we performed microsatellite analysis to detect UPD and MS-MLPA and/or aCGH analysis using custom made arrays for imprinted regions to detect submicroscopic CNVs. Next, we conducted aCGH analysis using catalog arrays to detect CNVs causing monogenic disorders in patients with normally methylated DMRs.

Results: Hypomethylation of the *H19*-DMR (*H19*-hypo) and UPD(7)mat which are the main genetic causes of SRS were detected 39, 10, and 9 patients in SRS-compatible, SRS-like, and non-SRS group, respectively. IDs other than SRS were detected 17, 3, and 4 patients in SRS-compatible, SRS-like, and non-SRS groups. TS14, UPD(20)mat, UPD(6)mat, PWS, and UPD(16)mat were detected 12, 5, 2, and 2 patients in this cohort. Various CNVs causing monogenic disorders were detected 11, 7, and 9 patients in SRS-compatible, SRS-like, and non-SRS group.

Discussion: SGA-SS is a heterogeneous condition. This study showed that a part of SGA-SS is caused by imprinting defects other than *H19*-hypo and UPD(7)mat or CNVs related to monogenic disorders. Our results highlight the clinical importance of imprinting defects and CNVs as genetic causes of SGA-SS.

RFC12.3

Imprinting defects and copy number variations in short children born small for gestational age

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Abnormal expression of imprinted genes leads to imprinting disorders (IDs). Silver-Russell syndrome (SRS) and Prader-Willi syndrome (PWS) are representative IDs showing small for gestational age and short stature (SGA-SS). Temple syndrome (TS14) caused by abnormal gene expression at the 14q32.2 imprinted region, maternal uniparental disomy of chromosome 6 (UPD(6)mat), 16 (UPD(16)mat), and 20 (UPD(20)mat) are also associated with SGA-SS. Furthermore, some copy number variations (CNVs) cause SGA-SS. However, there is no systematic study about IDs and CNVs in a large SGA-SS cohort.

Subjects: This study included 346 patients with SGA-SS and no apparent chromosomal or monogenic disorders. Their birth weight and length were less than the 10th percentile, and their height was less than -2.0 SD at two years of age. Of them, 148 patients with four or more items of Netchine-Harbison clinical scoring system (NH-CSS) were classified as SRS-compatible group, and 49 patients with three items of NH-CSS together with triangular face and/or fifth finger clinodactyly were classified as SRS-like group. The remaining 149 patients were classified as non-SRS group.

RFC12.4

NIPBL is required for postnatal growth and neural development

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Cornelia de Lange syndrome (CdLS) is a multisystem organ developmental disorder characterized by growth and cognitive deficits and premature aging, caused by mutations in genes coding for the cohesin complex. CdLS cells presented with gene expression dysregulation, genomic instability, decreased energy production and oxidative stress. Variants in the cohesin loading factor *Nipped-B-like* (*NIPBL*) gene can be identified in approximately 70% of cases and the severity of clinical presentation is closely correlated with the *Nipbl* expression levels determined by droplet digital PCR. In addition to the canonical role as cohesion loader, *Nipbl* is implicated in the regulation of gene expression, double strand DNA break repair and maintaining genomic stability. However, function of *Nipbl* in this syndrome is still unclear. To explore the role of *Nipbl* in postnatal brain development and function and the underlying mechanisms, we knocked out *NIPBL* postnatally in glutamatergic forebrain neurons using Cre recombinase driven by the Ca^{2+} /Calmodulin-dependent protein kinase II alpha gene promoter (Camk2a-Cre). Specific deletion of *nipbl* in the brain was validated by PCR. *NIPBL* cKO mice exhibited growth retardation and premature death compared to their heterozygous or *NIPBL* floxed littermates. Brain weight was significantly reduced in the *NIPBL* cKO knockout pups compared to that of the control mice. However, the brain weight to body weight ratio was significantly increased in the *NIPBL* cKO mice, suggesting that the reduction in brain weight is secondary to overall growth retardation. Although in open field testing no alteration in

mobility or anxiety-like behavior for *NIPBL* cKO mice, significant higher proportion of hind limb reflex was noted, which suggested impaired brain function. Histological analysis revealed mild cell disorganization in CA region of hippocampus without obvious abnormalities in the cortex of *NIPBL* cKO. Furthermore, TUNEL-positive cells were significantly increased in *Nipbl*-deficient brains. Immunostaining showed no significantly different GFAP expression in cortex and hippocampus between genotypes. In terms of gene expression, hundreds of mRNAs and non-coding RNAs were expressed at significantly different levels between *Nipbl*-deficient and control hippocampus. Further, a gene ontology analysis after RNA-sequencing suggested the downregulation of genes related to metabolic processes in the *NIPBL* cKO mice. Our results indicate that *Nipbl* regulate functional neural development, possibly by regulating gene expression. These findings may provide new insight to the management in CdLS.

RFC12.5

Cognitive and Neuroradiological assessments in Silver Russell patients

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Silver-Russell syndrome (SRS) is an epigenetic disorder characterized by severe intrauterine and postnatal growth retardation and typical dysmorphic features. The most common genetic abnormalities are 11p15 ICR1 loss of methylation, (11p15 LOM) and maternal uniparental disomy of chromosome 7 (mUPD7). There is little information on cognitive development in SRS patients and no neuroradiological studies are available so far. Global developmental delay and requirement for speech therapy have been reported in a few cases. It is known that IGF1/IGF2 axis, involved in the pathogenesis of SRS, plays a role in normal brain growth but little is known of the effect of SRS underlying molecular abnormalities on brain structure. We investigated a cohort of SRS children using cognitive assessment in conjunction with volumetric analysis and diffusion tensor imaging and compared the imaging findings with those of a cohort of controls. Aims: 1) Cognitive findings 2) Neuroanatomical features 3) to correlate genotype and phenotype..

Method: Neuropsychological assessments were performed in 31 patients (15 with UPD7, 15 with 11p15 LOM and 1 with cr11 duplication) followed in a single University Hospital center between 2015-2018. Brain MRI studies were performed on a 3Tesla scanner in SRS patients and in a group of 31 age-matched controls with normal brain MRI. The 3D-T1 weighted sequence was included in the scan protocol for all subjects. A Voxel-based morphometry analysis was performed on the 3D-T1-weighted sequences.

Results: The mean overall intelligence quotient (IQ) score was 86.5 ± 17 SD. Median Working Memory Index (WMI) and Processing Speed Index (PSI) were 91.3 ± 18 SD and 93.2 ± 19.3

SD without significant difference between the two groups. IQ, Verbal comprehension Index (VCI), Perceptual Reasoning Index (PRI) were significantly higher in 11p15LOM group than in UPD7 group at the age of 6-17 years ($p=0.01$). The single patient with 11cr duplication showed a cognitive delay; 59.3% of the subjects showed signs of attention deficit/hyperactivity disorder and 18.18% had learning difficulties. VBM analysis showed lower brain volume in SRS patients than controls at level of brain frontal poles (median 2.556 ± 0.401 SD cm³ and 2.989 ± 0.409 cm³, respectively; $P<.001$) and temporal poles (median 7.434 ± 1.354 SD cm³ and 8.304 ± 1.186 cm³, respectively; $P<.001$). The intrapatient analysis revealed a significant association between the volume of mesial temporal lobes and the WMI ($P=.002$). No significant differences in brain volumes were observed between UPD7 and 11p15 groups.

RFC12.6

Exploring the usefulness of a new type of pubertal height reference based on growth aligned or onset of pubertal growth

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Background: Height references have been available for decades, although only related to chronological age and not considering the broad individual variation in the timing and tempo of pubertal maturation and growth. Therefore, growth references and growth charts for the adolescent period have been of limited usefulness both for monitoring growth in individuals and for research. To fill this gap, we recently developed a new type of height reference based on growth curves aligned for onset of pubertal growth.

Aim: To explore the usefulness of this new type of pubertal height reference allowing alignment of individuals' growth curves based on timing of pubertal growth spurt.

Methods: References for total-height, specific-pubertal-height_{SDS} (P-function) and basic-height_{SDS} (QES-function) was constructed from QEPS (Quadratic-Exponential-Puberty-Stop)-function-estimated height curves aligned for time/age at onset of pubertal growth (defined as 5% P-function) from 1572 healthy GrowUp₁₉₉₀Gothenburg-cohort-children. Usefulness were explored using data from GrowUp₁₉₇₄Gothenburg-cohort children with different pubertal timing (early <-1.5 yrs, average ± 0.25 yrs, late $>+1.5$ yrs); tall/short stature; high/low BMI.

Results: When using height reference according to chronological age, the height curve was left-shifted for early and right-shifted for late maturers, highlighting the minimal usefulness of ordinary references only considering age.

When using the new puberty-adjusted references, the variation in total pubertal height gain (early maturers gaining more, late maturers gaining less compared to average pubertal maturers) was owing to differences between the three groups in basic growth whereas height gained owing to the specific pubertal function did

not differ between the three groups. Duration of pubertal growth was longer in early and shorter in late maturers and at adult height early matures were shorter whereas late male maturers were taller than those in the average group.

Tall children gain more height during puberty owing to more basic growth despite less specific pubertal growth, whereas short children gain less height during puberty due to less basic growth despite more specific pubertal growth (when compared to reference population).

Obese children have less specific pubertal height gain than thin children with an underlying low amount of specific P-function growth and more basic growth before puberty that was maintained during puberty (compared to reference population) whereas the opposite was found in thin children.

Conclusions: The new pubertal growth reference was able to identify differences in the underlying growth functions that translate into differences in total pubertal height gain for children of varying BMI, height, and different pubertal timings.

Adrenals and HP Axis

RFC13.1

Children and adolescents in the United States with congenital adrenal hyperplasia are not at increased risk for attention-deficit/hyperactivity disorder

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Background: Congenital adrenal hyperplasia (CAH) is a rare form of adrenal insufficiency characterized by impaired cortisol synthesis leading to excessive adrenal androgen production. Little is known regarding the effects of early and chronic androgen exposure in children with CAH, and whether this exposure may increase the risk of developing attention-deficit/hyperactivity disorder (ADHD) during childhood. The only study on the subject, based on a small sample of children and adolescents with CAH

(n=54), reported an increased rate of ADHD. The objective of the current study was to investigate the prevalence of ADHD in large administrative samples of insured children and adolescents with CAH compared to the general pediatric population in the United States.

Methods: We used the Treatment Pathways® interface to analyze data for individuals enrolled in employer-sponsored or public insurance plans with inclusion of pharmacy and mental health services claims in the IBM® MarketScan® Commercial and Medicaid Claims Databases. Subjects were included if they were continuously enrolled for ≥12 months from the first outpatient claim during October 2015–December 2017 and were between the ages of 5 and 18 years at that time. CAH prevalence was measured as the percentage of children and adolescents with ≥2 claims with E25.0 ICD-10 codes for CAH and ≥2 glucocorticoid prescriptions filled during the study period. ADHD prevalence was ascertained using a published claims-based algorithm. Subjects were stratified by age (5–11 years vs 12–18 years).

Results: The study period prevalence of CAH in the Commercial (N=3,532,914) and Medicaid (N=2,766,297) samples was 1/9,500 (n=373) and 1/14,000 (n=201), respectively. The prevalence of ADHD in the general population was 7.7% in the Commercial sample and 15.1% in the Medicaid sample. Among children and adolescents with CAH, there was no increase in risk of ADHD in either the Commercial (7.8% (n=29), odds ratio (OR)=1.01, 95% confidence interval (CI): 0.68–1.45, p=0.95) or Medicaid (13.9% (n=28), OR=0.91, 95% CI: 0.60–1.34, p=0.65) samples, as compared to the general population. ADHD prevalence did not differ significantly by age among those with CAH in either the Commercial or Medicaid samples.

Conclusions: Using two large national samples of privately and publicly insured children and adolescents with CAH in the United States, we found that the prevalence of medically-managed ADHD was comparable to that of the general pediatric population. These findings suggest that enhanced screening for ADHD among the pediatric CAH population may not be warranted.

RFC13.2

Development of novel non-invasive strategies for monitoring of treatment control in patients with congenital adrenal hyperplasia

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Introduction: Glucocorticoid treatment remains a challenging aspect in the management of congenital adrenal hyperplasia (CAH). Current strategies for monitoring treatment are suboptimal and rely largely on frequent blood tests, which are traumatising in children and young persons (CYP). Recent evidence indicates a crucial role of 11-oxygenated C19 androgens in the pathogenesis of CAH.

Aim: To explore the use of 11-oxygenated C19 androgens in non-invasive clinical tests to monitor glucocorticoid treatment in CAH.

Objective: To establish the correlation between plasma and salivary androgens in CYP with CAH.

Patients and Methods: We conducted a prospective multi-centre study recruiting CYP with CAH across the United Kingdom. Participants included 78 patients (43 females, 35 males, 8-18 years (12.87+/-3.04 years)) and 62 matched controls. Using liquid chromatography tandem mass spectrometry, we measured plasma and salivary concentrations for five steroid hormones: 17-hydroxyprogesterone, androstenedione, testosterone, 11-hydroxyandrostenedione and 11-ketotestosterone. The relationship between plasma and salivary steroids was analysed by Spearman correlation to assess their usefulness in clinical practice.

Results: Salivary and plasma concentrations correlated well for all the five steroids measured, with the strongest correlations found for androstenedione and 11-ketotestosterone:

androstenedione ($r_s=0.931$, $p<0.001$), testosterone ($r_s=0.867$, $p<0.001$), 17-hydroxyprogesterone ($r_s=0.871$, $p<0.001$), 11-hydroxyandrostenedione ($r_s=0.876$, $p<0.001$), 11-ketotestosterone ($r_s=0.944$, $p<0.001$). In addition, high correlations were found in CYP with CAH when analysing subgroups based on gender and age. Plasma and salivary steroid concentrations were significantly raised in patients compared to controls for all hormones, with the exception of testosterone which was higher in healthy individuals compared to CAH patients for the subgroup of pubertal boys. Analysing patients subgroups of CAH control based on 17-hydroxyprogesterone concentrations (<15 nmol/L; 15-30 nmol/L; >30 nmol/L), the strongest correlations between plasma and saliva were found for androstenedione and 11-ketotestosterone in both overtreated (androstenedione ($r_s=0.797$, $p=0.002$), 11-ketotestosterone ($r_s=0.888$, $p<0.001$)) and undertreated (androstenedione ($r_s=0.924$, $p<0.001$), 11-ketotestosterone ($r_s=0.878$, $p<0.001$)) CAH patients.

Conclusions: We have established that salivary concentrations correlate well with plasma concentrations for androgens used as markers of therapy control in CAH patients. Importantly, the best correlations were found for adrenal-derived 11-oxygenated C19 androgen 11-ketotestosterone as well as 17-hydroxyprogesterone and androstenedione, which are widely used for CAH monitoring. Thus, we believe that this novel and improved combination of salivary steroid hormones can serve as non-invasive monitoring tool in CAH providing a significant amount of additional information and will ultimately improve management and outcomes in CAH.

RFC13.3

Establishment of Reference Intervals for Hair Cortisol in Healthy Children Aged 0-18 Years Using Mass Spectrometric Analysis

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Background: Human scalp hair is a valuable matrix for determining long-term cortisol concentrations, with wide-spread applicability in clinical care as well as research. However, pediatric reference intervals are lacking. The aim of this study is to establish age-adjusted reference intervals for hair cortisol in children aged 0-18 years and to gain insight into hair-growth velocity in children up to 2 years old.

Methods: A total of 625 healthy children were enrolled through recruitment in pregnancy, infant-welfare clinics, and school visits. Scalp hair cortisol levels were measured using liquid chromatography-tandem mass spectrometry. Age-adjusted reference intervals were established. Hair-growth velocity was determined in children 0-2 years by measuring hair length with a 4 to 10 week interval.

Results: Hair cortisol levels were high (162.4 pg/mg) after birth with a sharp decrease in the first months of life, followed by a slow decrease until age 5 after which a subtle increase occurs until adult concentrations are reached at the age of 18 years (3.0 pg/mg). Average hair growth velocity measured in mm/months was significantly lower infants (0-6 months) compared to children (12-24 months) (3.5 versus 9.4, P<0.001).

Conclusions: This is the first study to provide age-adjusted reference intervals for hair cortisol in children from 0-18 years. Higher hair cortisol concentrations in infants might be explained by the significant lower hair growth rate in the first year of life. The establishment of pediatric hair cortisol reference ranges broadens the potential applications of this biomarker in both clinical practice and research.

Commentary: *The abstracts 225: Establishment of Reference Intervals for Hair Cortisol in Healthy Children Aged 0-18 Years Using Mass Spectrometric Analysis and 227: "Help my baby cries!" hair cortisol as marker for parental stress in excessive crying infants are an important part of my pHD trajectory concerning "early life stress" supervised by Dr Erica van den Akker. As hair cortisol analysis is increasingly being applied in both research and clinical practice, a combination of the results of these 2 abstracts would be very suitable for an oral presentation and interesting for both attending clinicians and researchers.*

ascertain its specific role adrenal cortex, siRNA NNT gene knock-down was performed in H295 adrenocortical cells to evaluate the effects on mitochondrial parameters and cortisol secretion (RIA).

Results: WES revealed the homozygous NNT p.G866D pathogenic variant in the affected patient. Family pedigree analysis confirmed the segregation of this variant with FGD in homozygosity. Heterozygous carriers (consanguineous parents and a young brother) were asymptomatic. Compared to wild-type (WT), both under basal and oxidative stress conditions, homozygous p.G866D NNT mononuclear leukocytes exhibited increased ROS production (p=0.02 and p=0.0001), decreased GSH levels (p<0.01 and p<0.001, r) and decreased mitochondrial mass (p=0.01 and p=0.001), respectively. Specific knockdown of the *NNT* gene in the H295 adrenal cells as shown by reduction of 55% and 50% in its RNAm protein levels did not change cell viability or cortisol secretion in basal condition. However, after 24h of treatment with 10uM forskolin, a potent stimulator of steroidogenesis, there was a marked decrease of cortisol production (p<0.0001).

Conclusion: Loss-of-function NNT mutations impair antioxidants mechanisms and affects the glutathione reductase systems, resulting in accumulation of reactive oxygen species. NNT impairment in adrenal cells decreases cortisol secretion. Altogether, these data explain the occurrence of adrenal insufficiency and confirm the genotype-phenotype association in patients carrying pathogenic NNT mutations.

RFC13.4

Loss-of-function NNT mutations impair antioxidants mechanisms and decreases cortisol secretion in patients with familiar glucocorticoid deficiency

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Background: The mitochondrial enzyme nicotinamide nucleotide transidrogenase (NNT) is essential in the antioxidant defense mechanisms and appears to be essential to the stages of adrenal steroidogenesis that occur inside the mitochondria.

Aim: To characterize how mutations in NNT gene impair adrenal steroidogenesis resulting in familial glucocorticoid deficiency (FGD).

Methods: Genomic DNA of a 1.8 years old boy with FGD was evaluated by whole exome sequencing (WES). Candidate genetic variants were analyzed *in silico* and confirmed by Sanger sequencing. Genotype-phenotype association of a new homozygous loss-of-function *NNT* variant with FGD was assessed *in vitro*. Several antioxidant mechanisms were evaluated under basal and oxidative induction conditions (100uM H2O2 by 5h) in transient cultures using leukocyte cells from the patient, the heterozygous family members and wild-type (WT) controls. Several mitochondrial parameters including reactive oxygen species (ROS) intracellular production (DCFDA), reduced glutathione (GSH; GSH-Glo Assay) and mitochondrial mass (Mitotraker) were analyzed. To

RFC13.5

Genetics of Familial Glucocorticoid Deficiency over the Decades: Phenotypic Variability and Associated Features

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Background: Over the last 25 years more than 410 cases with suspected Familial Glucocorticoid Deficiency (FGD) have been referred to our centre for genetic testing. All cases had low or undetectable serum cortisol paired with an elevated plasma ACTH level. Our patient cohort comprises 352 families from 30 different nationalities and ranges from neonates to patients in their eighties. Mutations in the *MC2R* were first discovered as causative of FGD in 1993, by candidate gene sequencing.

Objective and Methods: To determine the underlying cause of FGD by Sanger, targeted or whole exome sequencing techniques.

Results: A further 8 genes have been identified in our cohort in the temporal order of; *MRAP*, *STAR*, *MCM4*, *NNT*, *TXNRD2*, *SGPL1* and *CYP11A1*, made possible through advances in genetic techniques from homozygosity mapping to whole exome sequencing. *MC2R* mutations account for 25% of cases, *MRAP* for 20%, *NNT* for 8%, *STAR* for 7%, *CYP11A1* for 3% and *MCM4*, *TXNRD2* and *SGPL1* each for 1%. These genes are involved in diverse pathways and the resulting phenotypes are caused by defective ACTH signalling, cholesterol transport, steroidogenesis, cellular redox homeostasis, DNA replication or sphingolipid metabolism. The discovery of such genes, and subsequent functional assays of the respective proteins, have provided some explanation for the vari-

ability of the phenotype and association(s) with other co-morbidities. The work has highlighted 'mild' presentations of several adrenal insufficiency disorders, in particular non-classical presentations of lipid congenital adrenal hyperplasia and P450 side chain cleavage enzyme deficiency with partial loss-of-function variants in *STAR* and *CYP11A1* respectively. In addition, a few cases have revealed syndromic disease exemplified by the ethnically isolated population with a *MCM4* variant causing natural killer (NK) cell and glucocorticoid deficiency with DNA repair defect and *SGPL1* mutations which cause a syndrome of primary adrenal insufficiency, progressive renal dysfunction plus in some cases ichthyosis, hypothyroidism, immunodeficiency and neurologic defects.

Conclusion: With recent funding, we are currently analysing the long-term outcome of diagnosed individuals to study the evolution of features such as mineralocorticoid deficiency and pubertal progression. 34% of our cohort remains unsolved, to decipher whether the causative defects are in non-coding parts of known genes, are due to copy number variation or novel genetic aetiologies will form complementary future studies to improve the diagnosis of patients presenting with FGD.

RFC13.6

Inhibitory effects of curcuminoids on the enzymes from the steroidogenic pathway

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Background: Turmeric is a popular ingredient in the cuisine of many Asian countries. It is also known for its use in Chinese and Ayurvedic medicine. It comes from the root of the Curcuma longa. Turmeric is rich in curcuminoids, including curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Curcumin has potent anti-inflammatory and anti-carcinogenic activities. Since many anti-cancer drugs target enzymes from the steroidogenic pathway, we tested the bioactivity of curcuminoids on CYP17A1, CYP21A2, and CYP19A1 activities.

Methods: Curcuminoids were extracted from turmeric with organic solvents. We conducted a cell-based assay for CYP17A1 and CYP21A2 activities using human adrenal cell line NCI-H295R. ³H-pregnenolone was used for CYP17A1 assays, and ³H-17 α -hydroxyprogesterone was used as a substrate for CYP21A2. Curcuminoids were added at different concentrations and incubated for 24h. Steroids were separated by thin layer chromatography and analyzed by phosphorimager analysis. For CYP19A1 activity, an in vitro assay using endoplasmic reticulum from JEG3 were used with ³H-androstenedione as the substrate. Curcuminoids were incubated for 1h, and the formation of ³H-water from the androstenedione breakdown was measured by scintillation counting.

Results: The CYP17A1 hydroxylase activity, when using 10 μ g/ml of curcuminoids, was reduced to ~15%, whereas CYP17A1 lyase activity was reduced to ~30% of control. On the other hand, CYP21A2 activity was only reduced to a ~50%. Furthermore, CYP19A1 activity was reduced to 80~20% when using 1-100 μ g/ml of curcuminoids in a dose-dependent manner. No effect

on the activity of 5 α -reductase for conversion of testosterone to dihydrotestosterone was observed.

Conclusions: These studies show that curcuminoids may potentially cause some inhibition of steroid metabolism, especially at higher dosages. The activities of CYP17A1 and CYP19A1 were inhibited by curcuminoids which indicates potential the anti-carcinogenic effects in case of prostate cancer as well as breast cancer which can be targeted by inhibition of steroidogenesis. Also, the recent popularity of turmeric powder/curcumin as a dietary supplement needs further evaluation of the effect of curcuminoids on steroid metabolism.

GH and IGF1

RFC14.1

Papp-a2 deficiency results in sex-dependent modifications in hypothalamic regulation of energy homeostasis

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Pregnancy associated plasma protein (PAPP)-A2 is an insulin-like growth factor (IGF) binding protein (BP) protease that regulates IGF-1 availability affecting postnatal growth. Mutations in human *PAPP-A2* cause short stature and changes in bone size and mineral density. The present study aimed to characterize the effects of constitutive *Pappa2* gene deletion on hypothalamic regulation of energy homeostasis in adult male and female mice. In addition to being shorter, *Pappa2* knock-out (*ko/ko*) mice of both sexes weigh significantly less than their wild type (WT) controls. However, only male *Pappa2*^{ko/ko} mice were found to eat less ($p<0.01$) than same-sex controls during adulthood. Male *Pappa2*^{ko/ko} mice were also found to have an increase in energy expenditure ($p<0.05$) compared to their controls. These sex differences in affection of energy intake-output are most likely related to changes in hypothalamic factors controlling energy homeostasis as they were also modified in a sex-dependent manner. In *Pappa2*^{ko/ko} males the mRNA levels of the satiety-related factors leptin receptor (LEPR), cocaine- and amphetamine-regulated

transcript (CART) and proopiomelanocortin (POMC), as well as factors that stimulate appetite neuropeptide Y (NPY) and Agouti-related peptide (AgRP) were elevated in the hypothalamus. These changes in *Pappa2^{ko/ko}* male hypothalamus were accompanied by elevated mRNA levels of leptin in epididymal white adipose tissue (eWAT). In contrast, in *Pappa2^{ko/ko}* females the expression of the insulin receptor (INSR), CART and POMC were reduced in the hypothalamus and the expression of leptin and the thermogenic factor uncoupling protein 1 (UCP1) were reduced in eWAT.

In conclusion, energy homeostasis is affected in *Pappa2^{ko/ko}* mice in a sex-specific manner. However, how a reduction in IGF availability due to *PAPP-A2* deficiency modulates the development and functioning of hypothalamic metabolic circuits remains to be determined.

RFC14.2

Deciphering genetic aetiology among children born small-for-gestational-age with persistent short stature (SGA-SS): Phenotypic characteristics at diagnosis in a large single-centre cohort

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Background: SGA-SS is a heterogeneous condition defined as birth weight and/or birth length below -2SD for gestational age and postnatal height below -2.5SD, according to age-and sex-specific normative values. Despite being an indication for growth hormone (GH) therapy for 15 years, aetiology and prediction of treatment outcomes in most of SGA-SS children awaits elucidation.

Aim: To decipher genetic aetiologies among a large single-centre cohort of children born SGA and to define phenotypic characteristics at diagnosis in genetically defined subcohorts.

Patients/Methods: A single-centre cohort consists of 445 SGA-SS children (221 females; Turner syndrome was excluded) aged 1.3-27.0 years at this evaluation (median 11.8). We searched for genetic aetiology in majority of the cohort using individualised phenotype-based genetic techniques that included standard karyotyping, array comparative genomic hybridization (CGH), targeted or whole exome sequencing in selected individuals and methylation studies in phenotype of Silver-Russell syndrome (SRS).

Results: Thus far, genetic aetiology was elucidated in 60 children (33 females). Of these, 11 had a pathogenic variant of genes encoding cartilaginous matrix components (*ACAN* or one of genes encoding collagen structures [assigned here as *COL_X*]), 13 had *SHOX* defects, 9 had pathogenic genetic variants perturbing the GH-IGF-1 axis (*GHSR*, *HGMA2*, *OTX2*, *STAT3*, *IGFALS*, *IGF1R*), 10 had SRS, and 17 had miscellaneous single-gene or chromosomal conditions. Whereas the mid-parental height-SDS in children without known genetic aetiology (n=385) was -0.94 ± 0.04 (mean \pm SEM), parents were shorter in *ACAN/COL_X* (-2.10 ± 0.15 ; p<0.0001) and in *SHOX* (-1.51 ± 0.17 ; p=0.01) and

taller in SRS ($+0.17 \pm 0.27$; p<0.0001). SRS children tended to be born earlier (gestational week 36.2 ± 1.1 vs. 38.1 ± 0.2 ; p=0.06). Whereas the birth length in all subgroups was similar, birth weight-SDS was -1.96 ± 0.04 (mean \pm SEM) in SGA-SS children with undetermined aetiology but lower in SRS (-2.53 ± 0.25 ; p<0.05) and higher in *SHOX* (-1.31 ± 0.25 ; p<0.01). The postnatal growth failure was more pronounced in SRS (height-SDS at start of GH therapy -3.84 ± 0.41 ; p<0.05) than in SGA-SS children with undetermined aetiology (-3.06 ± 0.06), in *ACAN/COL_X* (-2.97 ± 0.14 ; n.s.), in *SHOX* (-3.02 ± 0.25 ; n.s.), and in the perturbed GH-IGF-1 axis (-3.13 ± 0.21 ; n.s.).

Conclusions: Subcohorts of SGA-SS children defined by genetic aetiology display specific phenotypic characteristics and differ in parental heights, gestational age, size at birth and severity of postnatal growth failure. These variables may facilitate predicting genetic background in some SGA-SS children. Nevertheless, in SGA-SS children genetic diagnosis remains a challenging task at the current level of knowledge.

RFC14.3

MicroRNAs change and target key regulatory genes involved in longitudinal growth in patients with idiopathic isolated growth hormone deficiency (IGHD) on growth hormone (GH) treatment

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The growth response in patients undergoing GH treatment is variable depending both on the patient's basal conditions and on personal innate sensitivity to therapy. MicroRNAs (miRNAs) are epigenetic regulators of gene expression, and are recognised as important regulators of biological and metabolic processes. It is unknown at present whether miRNAs could be early biomarkers of response to GH treatment in a perspective of individualised medicine, and whether they could disclose new information on the effects and regulation of GH.

We aimed at identifying all miRNAs varying on GH treatment using a global profiling approach, and at evaluating the principal pathways and biological processes, within growth, impacted by these miRNAs.

Ten prepubertal normal weight patients with IGHD were enrolled (5Males,5Females; CA:8,12 \pm 0,73yr). Global miRNA profiles (TaqMan Advanced Human CardA) were evaluated at -3, 0 and at +3 months on treatment. MiRNA expression levels at -3 and 0 months were compared and the miRNAs showing a p-value \leq 0.05 were excluded allowing to identify those miRNAs

changing only in response to treatment (+3 months) by either a factor $\text{Log}_{22}^{\text{DDCt}} > +1.5$ or $\text{Log}_{22}^{\text{DDCt}} < -1.5$ (up- or down-regulated, respectively). Single miRNA target genes were evaluated and DIANA-miRPathv3.0 software was used for *KEGG pathway* and *Gene Ontology* analyses.

Overall 30 miRNAs were regulated by GH, 27 were up-regulated, and 3 down-regulated. A subset of 8 showed the most stringent criteria. Interestingly, 13 miRNAs were specifically regulated in females only and other 13 in males only, suggesting gender-specific effects.

In the entire population, the miRNAs identified, targeted genes involved in the following pathways: ExtraCellularMatrix-receptor (COL1A1,COL2A1,integrins,laminins,SOX9,NF1 genes,etc.), Thyroid hormone(THReceptor,ATP1B2,MAP2K2,PIK3R2,RA F1,NOTCH2,AKT,CASP9,STAT1,FOXO1,MAPK1,etc.), Steroid biosynthesis, mTOR signaling (BRAF,AKT,PIK3CD,IGF1, PTEN,etc.), MAPK signaling (BRAF,SOS2,FGFR3,RAF1,FGF4,E GFR,TGFB1,FGF11,AKT, FLNB,FGF9,NF1,TGFB2,FGFs,FGFR s,TGFB3,etc.), Prolactin signaling (PRLR,STAT3,SOS2,SHC1,R AF1,AKT2,JAK2,SOCS1,FOXO3,STAT1,SOCS7,etc.), PI3K-Akt signaling (FGFR3,FGFR4,COL4A5,IGF1R,EGFR,COL5A1,COL 1A1, INSR, IGF1,VEGFB,FGFR1,FGF7,SOS2,RAF1,FGF8,etc.), Phosphatidylinositol signaling (PIK3R3,PTEN,etc.), and N-Glycan biosynthesis pathways.

Mutations of 15 of these genes are well known to cause genetic short stature in humans.

Furthermore, analyses of the biological processes identified the following as being regulated by the miRNAs identified: fibroblast growth factor receptor signaling, glycosaminoglycan metabolism, phosphatidylinositol-mediated signaling(FGFR3,IGF1R,PTPN11, IGF1,FGF8,FGFR1,etc.), insulin receptor signaling, transforming growth factor beta receptor signaling, androgen receptor signaling and the JAK-STAT cascade involved in GH signaling as expected.

In conclusion, GH regulates miRNAs that in turn regulate genes, pathways and biological processes involved with growth. Novel gender specific effects of GH were found. MiRNAs could be explored as biomarkers of response to treatment. Further, some novel genes implicated in the regulation of growth could be identified using this approach.

RFC14.4

GHR transcript heterogeneity may explain the phenotypic variability in patients with homozygous GHR pseudoexon (6Ψ) mutation

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Objectives: The homozygous *GHR* pseudoexon (6Ψ) mutation leads to aberrant splicing of the *GHR* gene with clinical and biochemical heterogeneity. We investigated whether the phenotypic variability could be explained by transcript heterogeneity i.e. ratio of abnormal (6Ψ *GHR*) to normal (WT *GHR*) transcripts and/or the presence of concurrent defects in other short stature (SS) genes.

Methods: 6Ψ *GHR* and WT *GHR* mRNA transcripts from 4 6Ψ patients, fibroblasts (height SDS -3.6, -3.4, -4.2 and -3.8) and 1 control subject were investigated by reverse-transcriptase PCR (RT-PCR) using intron skipping primers. Transcripts (mean±SD) were quantified by qRT-PCR and double delta CT analysis (5 experimental repeats) and compared using ANOVA with Bonferroni correction. In eleven 6Ψ patients, 63 genes known to cause SS were analysed by targeted sequencing.

Results: RT-PCR confirmed the presence of WT transcript (193 bp) in 6Ψ patients and control. 6Ψ transcript (217 bp) was seen in all 4 6Ψ patients but not control. Direct sequencing verified predicted mRNA sequences. 6Ψ transcript expression was significantly different amongst patients (1 ± 0 , 0.334 ± 0.032 , 0.549 ± 0.005 , 0.960 ± 0.071) p values<0.001, except between patients 1 & 4. The mean 6Ψ:WT transcript ratios (40.33, 29.69, 72.74, 47.39) correlated negatively with height SDS ($R=-0.96$, p value <0.01) in all 4 6Ψ patients.

Genetic analysis of 11 6Ψ patients revealed 9 deleterious variants in 6 genes. However, there was no correlation between the number of gene hits and degree of short stature in individual 6Ψ patients.

Conclusion: Varying amounts of 6Ψ and WT *GHR* transcripts were identified in 6Ψ patients, with no 6Ψ transcript identified in the control. A higher 6Ψ:WT *GHR* transcript ratio correlates with the severity of short stature and thus may explain the phenotypic variability. Genetic changes in other known SS genes do not appear to account for the phenotypic variation.

RFC14.5**Bioactive IGF-I concentration compared to total IGF-I concentration before and after 1 year of high-dose growth hormone in short children born small for gestational age - North European SGA Study (NESGAS)**

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Background: Children born small for gestational age (SGA) exhibit wide variations in the activity of growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis and this heterogeneity may result in supra physiological concentrations of IGF-I during GH treatment. The long-term effects of elevated IGF-I levels has been a matter of concern. We explored the variations in total IGF-I and bioactive IGF-I and the associations with growth and glucose metabolism in response to a fixed GH dose over 1 year in SGA children.

Methods: The North European Small for Gestational Age Study (NESGAS) is a multicenter study (n=101, 61 males) of GH therapy in prepubertal short SGA children. They received GH therapy at 67 μ g/kg/day for 1 year. IGF-I was measured by a commercial immunoassay and bioactive IGF-I was measured using the IGF-I kinase receptor activation assay (KIRA).

Results: Bioactive IGF-I at baseline was significantly lower among boys compared to girls (median (25-75 percentile) (-1.4SDS (-2.7 to -0.2)) and -0.2SDS (-1.4–0.4), respectively) (p=0.002). In contrast, no difference in bioactive IGF-I SDS according to gender was present after one year of GH treatment. No significant differences in total IGF-I were found between the genders before and after one year of high-dose GH treatment.

Bioactive IGF-I (SDS) was significantly correlated to height (SDS) at baseline and the association was stronger than the correlation between total IGF-I (SDS) and height (r :0.29, p=0.005 and r :0.17, p=0.10, respectively). After one year of high-dose GH treatment 68% (N=65) of the children in the entire cohort had increased levels of total IGF-I above + 2SD, whereas only 15% (N=15) had levels of bioactive IGF-I above the normal reference. Change in height (SDS) correlated significantly with baseline total IGF-I (SDS) (r :0.25, p=0.02) but not with bioactive IGF-I (SDS) (r :0.11, p=0.30). Bioactive IGF-I (SDS) correlated positively with total IGF-I (SDS) (r :0.35, p=0.001) and IGFBP-3 (SDS)

(r :0.26, p=0.01) and correlated negatively with insulin sensitivity (HOMA-S) (r :0.29, p=0.007) and IGFBP-1 (r :0.18, p=0.08).

Conclusion: Bioactive IGF-I showed a stronger association with height compared to total IGF-I at start, but was not a good predictor of the one year response to high-dose GH treatment. Reassuringly, we found that only 15 % of the GH treated SGA children had supra-physiological levels of bioactive IGF-I after one year of high-dose treatment in contrast to elevated total IGF-I levels in 68% of the patients.

RFC14.6**Growth Hormone Deficiency (GHD): Assessing Burden of Disease in Children and Adolescents: the Growth Hormone Deficiency – Child Impact Measure (GHD-CIM)**

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Background: Children with growth hormone deficiency (GHD) may have to deal with practical, emotional, and functional difficulties. Unfortunately, to date, there is no condition specific measure of the impact of GHD for these children. The Growth Hormone Deficiency – Child Impact Measure (GHD-CIM) was developed according to FDA/EMA guidances to address this gap. There are two GHD-CIM versions: child self-report (PRO) for ages 9 to <13 years and observer-report (ObsRO) for parents/guardians of children 4 to <9 years. Items are based on qualitative interviews with 39 children and 31 parents. This study presents the GHD-CIM psychometric validation results.

Methods: A non-interventional, multi-clinic-based validation study (US and UK) of pre-pubertal children with GHD and parents/guardians of similar children was completed. Psychometric analyses were conducted according to an a-priori statistical analysis plan to determine the measurement model, reliability, validity, responsiveness, and the minimally important difference (MID).

Results: The analytic data set was 243 subjects (145 children and 98 parents/guardians). Children's average age was 9.2 years, they were 72% male, and average age at diagnosis was 6.9 years. Item reduction resulted in a 20-item measure. Factor analyses identified 3 domains: Physical Functioning, Social Well-being, and Emotional Well-being. Internal consistency reliability was acceptable for all domains and the Overall score (Cronbach's alpha >0.70) as was test-retest reliability for the Emotional and Overall (above 0.70) although test-retest reliability was slightly lower than expected for the Physical (0.59) and Social (0.65). At least one of the convergent validity hypotheses for each domain and Overall was proven (r > 0.40). Known groups validity hypotheses for the Emotional and Social Well-being domains were significant (p <0.05) and a trend for the Physical Functioning and Overall. All GHD-CIM domains and Overall were able to significantly discriminate between levels of emotional well-being. Associated effect sizes ranged from -0.44 to -0.49, indicating that the GHD-CIM is sensitive to change. Anchor based patient and clinician ratings of severity of disease

suggest a preliminary MID of 5 points for the Overall score, 5 for Physical Functioning, 7 for Emotional Well-Being, and 5 for the Social Well-Being domains.

Conclusions: The GHD-CIM was found to be reliable and valid and is considered ready for inclusion in clinical trials and clinical practice. Accurate and reliable assessment of disease burden can help researchers and clinicians better assess and address impacts of disease, factors that may affect treatment compliance, and may improve doctor-patient communications.

than the PBS-injected mice and was 85% of the wild type control mice. Urinary cAMP measurements at 4 months showed a non-significant diminution in the treated mice. Despite the observed effect in skeletal growth and renal physiology, the small number of mice in each group did not allow statistics to be significant. Further studies are needed to confirm our observation in a larger group of diseased mice followed 1 yr and to study the skeletal and renal expression of the vector.

Although yet preliminary, the current data are encouraging for attempting gene therapy in various genetic bone diseases if it may improve patients' clinical status.

Late Breaking Abstracts

RFC15.1

Preclinical Studies of Acrodysostosis Gene AAV Therapy in a Knock-In R368X PRKAR1A Mouse Model

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The use of recombinant adeno-associated viruses (rAAV) as safe vectors have allowed hundreds of gene therapy attempts to treat monogenic diseases not including bone genetic diseases (Gao G, Nat Rev Drug Dis 2019). To our knowledge, there has been few attempts to apply gene therapy to monogenic bone diseases, largely because most skeletal malformations are being developed during fetal life. Patients affected with acrodysostosis are known to aggravate their skeletal malformations during postnatal development and to suffer from various organ dysfunctions related to the impairment of the PKA pathway.

We have produced an acrodysostotic mouse model as a knock-in (KI) of the recurrent R368X mutation to characterize phenotypic traits and attempt their correction with gene therapy. Heterozygous mice recapitulate the major phenotypic traits of the human disease, notably the skeletal and renal abnormalities (Le Stunff, J Bone Min Res 2017). Herein we report our preliminary observations of the use of rAAV in this model. We designed a therapeutic cassette made of the CAG promoter and the human PRKAR1A cDNA (single strand). We validated the function of this cassette by plasmid transfection in HEK cells, then produced a AAV9 vector carrying this cassette. At 1 month of age, KI R368 mice were injected intravenously with 2×10^{13} vg/kg (n=9) or PBS (n=8). Littermate WT mice (n=11) were sham injected as controls. Mice were kept alive to follow phenotypic traits, thus we do not have yet data about biodistribution and expression of the vector in body tissues.

Our preliminary results show that after 6 months of follow-up, the growth of the vector-injected mice was 15-20% more rapid

RFC15.2

BMP4 mutations as a novel cause of normosmic hypogonadotropic hypogonadism

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BMP4, a member of the bone morphogenetic protein family which is part of the transforming growth factor-beta superfamily, is involved in the embryonic development of various organ and tissues including the cranio-facial structures, olfactory placode, pituitary, eyes, heart, and kidneys. Mutations in this gene are associated with orofacial cleft and microphthalmia in human patients. *BMP4* plays an important role in the embryonic development of the GnRH neurons (Forni et al 2013, Layman et al 2011) and anterior pituitary by regulating diverse cellular responses, such as cell differentiation, migration, adhesion, and proliferation (Massague et al 2000). *BMP4* also has been described as particularly inhibiting FSH production (Nicol et al 2008). Recently, a heterozygous truncating mutation was described in a 6 years old pre-pubertal age child with combined pituitary hormone deficiency (Rodriguez-Contreras et al 2019). Mutations in the BMP genetic network including *BMP4* were reported to be found in patients with hypogonadotropic hypogonadism (HH) in a meeting abstract (Cassatella et al ASHG 2013). However, no detailed description of *BMP4* mutations in the etiology of HH has been found in the literature. Here we present three independent patients with isolated HH apparently due to deleterious sequence variants in *BMP4*.

Methods: We screened the whole exome sequencing data from 215 HH patients.

Patient number	DNA change	Zygosity	Protein change	Minor allele frequency in gnomAD	CADD score
1	NM_001202.3:c.450C>G	Hom	NP_001193.2:p.(Asn150Lys)	0.00001	22.5
2	NM_001202.3:c.41G>A	Het	NP_001193.2:p.(Cys14Tyr)	0.00001	24.9
3	NM_001202.3:c.751C>T	Het	NP_001193.2:p.(His251Tyr)	0.0001	29.6

Results: We identified apparently deleterious rare *BMP4* sequence variants in three independent patients with HH. All patients were normosmic. The patients did not have deficiencies of other pituitary hormones. These variants were not found in in-house controls. Variant p.N150K was found in homozygosity in a patient from a consanguineous family. Interestingly, this same variant has been reported to cause renal hypodysplasia in heterozygosity as well as homozygosity in two independent patients (Weber et al 2008). In all three patients both FSH and LH were similarly deficient, i.e. there was not a particularly more pronounced deficiency of FSH over LH. Functional studies have been planned.

Conclusions: These results strongly suggest that inactivating variants in *BMP4* are novel causes of normosmic hypogonadotropic hypogonadism. This phenotype is consistent with previously described role of *BMP4* in the ontogeny of the GnRH neurons and the anterior pituitary.

RFC15.3

Metformin treatment affects ACTH receptor activation and downstream signaling: a potential treatment for ACTH excess disorders and management of hyperandrogenic states

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Background: The peptide hormone adrenocorticotropin (ACTH or Corticotropin) is a major component of the stress response system in the Hypothalamus-Pituitary-Adrenal (HPA) axis. Under stress, it is secreted from the anterior pituitary and stimulates cortisol production from the adrenal cortex. Changes in ACTH production or action are associated with multiple disease conditions. In clinical situations like Cushing's disease, ectopic ACTH syndrome and congenital adrenal hyperplasia, there is excess ACTH production and blocking the interaction of ACTH at its site of action would be a therapeutic option. Currently, effective therapy to block the action of ACTH is unavailable. Insulin-sensitizing treatment, such as metformin, has been used to ameliorate a few reported cases of adrenal disorders. However, the exact mechanism of how these insulin-sensitizing drugs affect the HPA axis is not known.

Aim: To test whether insulin-sensitizing drugs have a direct effect on the activity of ACTH.

Methods: *In-vitro* assays were performed to test the effect of metformin on ACTH receptor activation and signaling. For assays, the OS3 cells transfected with ACTH receptor and luciferase reporter plasmids were used, and cyclic AMP (cAMP) was measured by luciferase assay. The potential to shift the ACTH concentration-response curve (CRC) was evaluated to characterize the antagonist activity of metformin. Detailed characterization was done to calculate the 50% inhibitory concentration (IC_{50}) by varying concentration of metformin.

Results and conclusion: Metformin was found to inhibit the activation of the ACTH receptor and downstream signaling associated with ACTH response. Significant inhibition of ACTH

induced receptor activation upon treatment with 10 mM metformin was observed. Metformin shifted the ACTH CRC towards the right by half log, indicating antagonism. This study could be useful in developing new strategies for management of hyperandrogenic states.

RFC15.4

Clinical and genetic characterization of 148 patients with persistent or transient congenital hyperinsulinism: a population-based study in Finns

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Context: Major advances have been made in the genetics and classification of congenital hyperinsulinism (CHI; OMIM #256450).

Objective: To examine the molecular and clinical characteristics of the Finnish patients with persistent and transient CHI.

Design A cross-sectional study with the register data and targeted sequencing of 104 genes affecting glucose metabolism.

Patients: Genetic and phenotypic data were collected from 148 patients with persistent (n=92) and transient (n=56) CHI diagnosed between 1972 and 2015. A total of 88 patients with persistent and 56 with transient CHI were included in the analysis of 104 genes affecting glucose metabolism, including ten CHI-associated genes.

Main outcome measures: Targeted next-generation sequencing results and genotype-phenotype associations.

Results Six novel and 20 previously reported pathogenic or likely pathogenic variants in *ABCC8*, *KCNJ11*, *GLUD1*, *GCK*, *HNF4A* and *SLC16A1* genes were found in 70% (n=64) and 0% of the patients with persistent and transient CHI, respectively. K_{ATP} channel variants explained 58% of the mutation positive cases.

Conclusions: K_{ATP} channel gene mutations explained a majority of the genetic etiology of CHI in our study. Genotype-phenotype associations showed wide phenotypic diversity. Therefore, next generation sequencing should be applied in the diagnostics of CHI.

RFC15.5**De novo missense mutation in SP7 in a patient with cranial hyperostosis, long bone fragility, and increased osteoblast number**

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Background: Sp7, also known as Osterix (Osx), is a zinc-finger transcription factor, essential for osteoblast differentiation and bone formation. While bone formation is absent in Osx knockout mice, human loss of function mutations lead to impaired bone formation and cause recessive osteogenesis imperfecta, type XII (OMIM 613849).

Case: The 5-year-old son of non-consanguineous parents presented with multiple long bone fractures due to bone fragility, scoliosis, remarkably thickened calvarium, craniosynostosis, and heterogeneity of long bone cortical thickness. Elevated serum alkaline phosphatase and Tartrate-resistant acid phosphatase (TRAP5b) indicated an increased bone turnover, while linear growth and psychomotor development remained unaffected.

Results: Iliac crest biopsy confirmed increased bone turnover with elevated osteoblast number, osteoid thickness, osteoclast number, and decreased bone matrix mineralization. Exome sequencing, confirmed by Sanger sequencing, on the proband and his parents, identified a *de novo* rare missense mutation in SP7 (c.926C>G:p.S309W) which was predicted to be deleterious by multiple silico analyses.

To test the impact of the SP7 variant, we infected mouse primary chondrocytes and mesenchymal stem cells with retrovirus expressing GFP (as a negative control), wild-type (WT) SP7, or the S309W SP7 variant, followed by induction of osteoblast differentiation. S309W SP7 resulted in an aberrant expression profile: elevated endogenous *Sp7* and *Col1a1* and decreased *Sox9* and *Col2a1* mRNA as compared both to GFP and WT, suggesting accelerated osteoblast differentiation, while decreased expression of *Mmp13*, *Ibsp*, and *Bglap* indicated impaired bone matrix formation.

Heterozygous knock-in mice carrying the S309W variant showed perinatal lethality, but a small number of mice were recovered. Micro-CT showed increased bone thickness in clavicles, ribs, and long bones. Trabecular bone density was decreased at

the metaphyses but increased at the diaphyses. Marrow space was almost completely absent in the long bones in a mosaic heterozygous 20-week mouse.

Discussion: A previously reported frameshift mutation in SP7 in humans caused recessive osteogenesis imperfecta, and biallelic knockout in mice caused lack of bone formation. In contrast, our patient showed a markedly different dominant phenotype, with evidence of elevated osteoblast numbers and heterogeneously increased bone formation but defective osteoblast function. Mice with this mutation also showed a dominant phenotype with increased bone formation. Taken together, the findings suggest that the SP7 variant in this patient is not a simple loss-of-function mutation causing a failure of osteoblast differentiation but instead causes more complex alterations in osteoblast differentiation.

RFC15.6**Absence of puberty and estrogen resistance by estrogen alpha receptor inactivation in two sisters: a mutation for variable phenotypic severity**

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Introduction: Estrogens play an essential role in reproduction and their peripheral action is mediated via nuclear alfa and beta receptors (ER) as well as membrane receptors. To date, only 3 females and 2 males from 3 families with a loss of function of ER α have been reported. The phenotype in these families was strongly suggestive of an estrogen resistance with an absence of a complete puberty, a delay in epiphyseal maturation with high estradiol levels and elevated gonadotropin levels.

Goal: The objective of this study was to describe a new family in which 2 sisters displayed different levels of endocrine and ovarian defects although they carried the same homozygous rare variant in the ER α -encoding ESR1 gene.

Materials and methods: A 36-year-old woman with a primary amenorrhea and no breast development, had elevated 17 β -estradiol (1497 pg/ml), high FSH (57 IU/L) and LH (21 IU/L) plasma levels, and enlarged multifollicular ovaries (11 and 17 ml). Her 18-year-old sister did not enter puberty and had moderate increases in 17 β -estradiol (204 pg/ml) with high FSH (29 IU/L) and LH (22 IU/L) plasma levels and ovaries of normal size. The parents are consanguineous.

Results: In both cases, genetic analysis identified a homozygous variant of ESR1 (c.1154A>T) leading to the substitution of the highly conserved glutamic acid at position 385 by a valine (p.Glu385Val). Both parents as well as an unaffected sister were heterozygous for the variant. The Glu385 is located in the ligand binding domain and the in-silico analysis predicted a deleterious effect on the protein function. Modeling study of the ER α -E385V

variant showed a slight displacement of the H-12 helix, which plays a crucial role in signal transmission, suggesting that the Glu385Val replacement might preclude the activation of the receptor.

A functional analysis was performed by transient expression of WT-ER α or Glu385Val-ER α in HEK293A cells. Glu385Val-ER α transfected cells showed a strong decrease in transcriptional activation by 17 β -estradiol of a reporter gene controlled by a standard estradiol-responsive-element as well as a milder inhibition of the KISS1 promoter when compared to WT-ER α . Immunofluorescence analysis showed lower nuclear translocation of E385V-ER α in the presence of 17 β -estradiol as compared to WT-ER α .

Conclusion: These two new cases are remarkable as they are sisters and they display a different level of severity of the ovarian and hormonal phenotypes. This phenotypic discrepancy could be attributable to a mechanism that could partially compensate the ER α inactivation.

Prize Winners

HA1

Development of testicular organoids to understand Disorders of Sex Development

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Disorders of sex development (DSD) constitute an array of rare disorders affecting the genito-urinary tract and the endocrine-reproductive system and are often identified in the newborn or adolescent. Gene mutations causing DSD are slowly being identified using high-throughput sequencing, but the interpretation of the data and ascribing causality to novel variants is challenging. This is because DSD mutations occur in multiple genes with each gene affecting a small number of individuals and suitable animal/cellular models that accurately reflect the physiopathology of DSD are lacking. To establish causality of genetic variants causing DSD and understand the mechanisms of disease development and progression we have developed multiple novel models by cellular reprogramming.

One of the novel *ex-vivo* cellular models we have developed involves directed differentiation of human induced pluripotent stem cells (iPSCs) into somatic cells of the XY or XX gonad using defined conditioned media. Briefly, 46,XY iPSCs are subjected to directed differentiation sequentially using a conditioned medium containing defined concentrations of bFGF, BMP4 and retinoic acid and insulin transferrin selenium. The iPSCs derived from a healthy male can differentiate to the mesoderm and intermediate mesoderm (IM), as indicated by the expression of stage appropriate markers. The IM undergoes mesenchymal-to-epithelium transition and eventually results in formation of foetal Sertoli-like cells. These cells express Sertoli specific transcripts and have the ability to self-aggregate and form tubule-like structures similar to embryonic Sertoli cells. When these protocols are applied to iPSCs with a 46,XX chromosome complement, the resultant population shows

a granulosa-like profile. We have also derived iPSCs from erythroblasts of a 46,XY individual with complete gonadal dysgenesis due to a missense mutation in NR5A1. When these cells undergo similar differentiation protocols, we observe an aberrant expression profile and an inability to form tubular structures. For optimal recapitulation of both the structure and function of the developing embryonic testis, we are developing a gonad-on-chip device that realizes the self-organization of iPSC derived Sertoli cells within a perfusible microfluidic device. Our new model is a powerful tool to investigate patient-specific atypical transcription networks as well as provide mechanistic insight into the stage specific dysregulation of signaling, associated with mutations causing DSD.

HA2

Partial CRISPR/Cas9 IL1R1 & IFNGR1 Knock-Down Improves β -cell Survival And Function Under Cytokine-Induced Inflammation

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Type 1 diabetes (T1D) is a chronic disease characterized by the autoimmune destruction of pancreatic β cells. This destruction is mediated by lymphocytes T helper and cytotoxic, and by the action of the pro-inflammatory cytokines IL1 β , IFN γ and TNF α inside the islets of Langerhans. We propose a new approach to alleviate islet inflammation by targeting pro-inflammatory cytokine receptors. Our hypothesis is that the downregulation of inflammatory pathways may improve β cell survival in the context of inflammation after T1D onset. We knocked-down IL1R1 or IFNGR1 receptors in the MIN6 β -cell line by using the CRISPR/Cas9 gene editing system. GuideRNA targeting the extracellular domain of the transmembrane receptors IL1R1 and IFNGR1 were designed and cloned into pSpCas9(BB)-2A-GFP plasmid. The knockdown efficiency was evaluated by flow cytometry and qPCR, and ranged from 12 to 40%. MIN6 or CRISPR-MIN6 were treated with IL1 β or IFN γ during 48 h at 5 or 10 ng/mL. Cell viability of CRISPR-IFNGR1 cell lines evaluated by MTT assay was improved after IFN γ exposure compared to naive MIN6 (107 ± 19.3 and 89.7 ± 22.7 vs $76 \pm 22.1\%$; $P = 0.09$ and 0.04) whereas cell viability of CRISPR-IL1R1 cell line tended to be improved after IL1 β treatment (136 ± 33.6 vs $80 \pm 11.0\%$; $P = 0.13$). The assessment of insulin secretion capacities of CRISPR-MIN6 cells showed higher secretion rates (0.61 ± 0.18 vs 0.19 ± 0.06 ng insulin/ μ g protein; $P = 0.04$), as compared to appropriate controls. Gene expression of the pro-apoptotic receptor Fas was decreased inside the CRISPR-MIN6 cell lines and the expression of the pro-inflammatory cytokine Il6 gene was decreased inside the CRISPR-IL1R1 cell line, as compared to MIN6 control. Similarly, gene expression of ER stress markers Atf4 and Chop decreased inside the CRISPR-IL1R1 and CRISPR-IFNGR1 cell lines, respectively, as compared to controls. Our results show that the targeting of IL1R1 or IFNGR1 could protect pancreatic β cells from the inflammatory attack found in T1D by decreasing apoptosis, inflammation and ER stress. Our results are encouraging and require the development of the three-cytokine receptor (IL1R1, IFNGR1 and TNFR1) knockdown to fully address the potential of this system to be translated into

clinical research protocols. The possibility of a translational perspective of our knockdown system is suggested by the ongoing clinical trial using the CRISPR/Cas9 system to evaluate the safety of PD-1 knockout engineered T cells in treating metastatic non-small cell lung cancer (NCT02793856).

Top 20 Poster

T1

Circulating miR-451a: a biomarker to guide diagnosis and treatment of polycystic ovary syndrome in adolescent girls

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Polycystic ovary syndrome (PCOS) is a prevalent disorder in adolescent girls, commonly driven by hepato-visceral fat excess, usually presenting with hirsutism and menstrual irregularity, and often followed by subfertility and type 2 diabetes.

We studied the miRNA profile of adolescent girls with PCOS, and the effects of randomized treatment with an oral contraceptive (OC) or with spironolactone-pioglitazone-metformin (SPIOMET, aiming at loss of hepato-visceral fat excess) for 1 year. Post-treatment ovulation rates were assessed by salivary progesterone. The miRNA profiling was performed by RNA sequencing, differentially expressed miRNAs being validated by qRT-PCR in 13 control and 31 PCOS girls.

Girls with PCOS had markedly reduced concentrations of circulating miR-451a, miR-652-3p, miR-106b-5p and miR-206; pathway enrichment analysis showed that these miRNAs target genes involved in energy homeostasis and cell-cycle control. In the present study, miR-451a could diagnose PCOS (versus a healthy condition) with 100% sensitivity and 100% specificity. SPIOMET (but not OC) was accompanied by on-treatment normalization of the miRNA profile in PCOS girls; miR-451a concentrations after 1 year on OC or SPIOMET treatment associated closely ($r=0.66$; $P<0.0001$) with post-treatment ovulation rates.

In conclusion, circulating miR-451a may become a biomarker contributing to guide the diagnosis and treatment of PCOS in adolescent girls.

T2

Assessment of ZnT8 antigen in thyroid cells in children and adolescents with Hashimoto thyroiditis and nodular goitre

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Introduction: The presence of ZnT8 (zinc transporter 8) has been described on the surface of beta pancreatic cells in type 1 diabetic patients and the ZnT8 Ab (zinc transporter-8 autoantibody) has been recently established as a new marker of this autoimmune disease. There are studies demonstrating that ZnT8 may be of importance in some other endocrine cell types. In our study we wanted to verify the presence of ZnT8 in thyroid cells of children and adolescents with autoimmune thyroid diseases (AITDs) and nodular goitre to investigate the potential contribution to the pathophysiology of the diseases.

Material and Methods: The study was performed in the group of 29 children and adolescents (6 boys and 23 girls) (44 nodules): 24 Hashimoto thyroiditis patients (mean age 14.9 ± 3.0 years) and 21 nodular goitre with lymphocytic thyroiditis patients (mean age 14.1 ± 3.3 years). Patients were recruited from the Paediatric Endocrinology Outpatient Clinic, Medical University of Białystok. ZnT8 antigen on the surface of thyroid cells obtained during fine needle aspiration biopsy was detected immunohistochemical method with monoclonal mouse origin antibody ZnT-8 (B-9): sc-514715 Santa Cruz Biotechnology. The immunohistochemical reaction was assessed with light microscope. The result was presented in a following scale: light colour (+) – weak reaction, light brown colour (++) – mild reaction, dark brown colour (+++) – strong reaction.

Results: The presence of ZnT8 antigen was detected in follicular thyroid cells and oxyphilic cells. Follicular cells in Hashimoto's thyroiditis revealed weak reactions with antibodies (+) in 60%, mild reactions (++) in 30%, and strong reactions (++) in 10% while oxyphilic cells revealed mild reactions (++) in 55%, strong reactions (++) in 30%, and weak reactions (+) in 15%. In nodular goitre follicular cells revealed in most cases strong reaction (++).

Conclusions: In conclusion, these results suggest that in case of an intensive infiltration with lymphocytes (Hashimoto thyroiditis) the oxyphilic cells reveal higher expression of ZnT8 antibody (stronger reaction) than follicular cells. On the other hand ZnT8 is highly expressed in follicular cells in the nodular goitre.

T3**Hypothalamus and Pituitary Gland Antibodies in Childhood-Onset Brain Tumors and Pituitary Dysfunction**

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Background: Antipituitary (APA) and antihypothalamus antibodies (AHA) have not been investigated in children and adolescents with brain tumors.

Patients and Methods: Sixty-three patients with craniopharyngioma, glioma and germinoma treated with surgery and/or chemotherapy and/or radiotherapy were evaluated at a median age of 13 years. Forty-one had MPHD, 6 had a single defect being GH the most common (65.1%), followed by AVP (61.9%), TSH (57.1%), ACTH (49.2%) and gonadotropin (38.1%). APA and AHA were evaluated by indirect immunofluorescence in patients and in fifty controls.

Aim: To detect the presence and role of APA and AHA in patients with craniopharyngioma, glioma or germinoma treated with different modalities.

Results: APA+ and/or AHA+ were detected in half of the patients but not in the controls ($P<0.001$); 25 were APA+ ($P=0.001$), 26 were AHA+ and 20 were both APA+ and AHA+ ($P<0.001$), mostly with germinoma. APA+ ($P<0.001$) and their titers ($P=0.008$) were significantly associated with the number of pituitary defects, with a 25% risk of developing an additional pituitary defect at each increase in antibody titers from one level to a higher one; this risk was confirmed also after correction for tumor type (18.4%, $p=0.002$). A similar relation was found for AHA+ ($P=0.028$). There was a significant association between the presence of APA+ and radiotherapy ($P=0.03$).

Conclusion: Patients with germinoma are prone to develop an autoimmune process involving the pituitary gland and the hypothalamus that contributes to endocrine dysfunction. Attention should be paid to avoid misdiagnosis of germinoma masked by an autoimmune pituitary condition.

T4**Use of stored serum in the study of time trends and geographical differences in exposure of pregnant women to phthalates**

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Background: There is increasing evidence from epidemiological studies that some man-made chemicals present in the environment can disrupt endocrine homeostasis in exposed humans. Exposure during foetal life to e.g. phthalates has been linked to adverse effects on testicular and ovarian development, thyroid homeostasis and growth in postnatal life. Exposure to phthalates fluctuates not only from day to day but also over time which poses a major challenge for exposure classification. Urine concentrations are currently considered the best proxy of phthalate exposure. However, many longitudinal mother-child cohorts which aim to investigate long-term health consequences of the foetal environment may have biobanks with only serum samples. In serum samples, phthalate levels are generally lower and there may be an unknown contribution from post-collection contamination.

Objectives: To explore whether prenatal maternal serum samples can be used to assess phthalate exposure. Additionally, to investigate temporal and geographical differences in phthalate exposure across three different birth cohorts.

Methods: We compared phthalate metabolite levels in prenatal serum samples from an Australian (1989-91) and a Danish (1997-2001) birth cohort with levels in serum and urine samples from a recent Danish birth cohort (2012-14). Samples were analysed for 32 phthalate metabolites from 15 phthalate diesters by isotope-diluted liquid chromatography-tandem mass spectrometry (LC-MS/MS) in the same laboratory.

Results & Discussion: Significant differences in phthalate metabolite levels between the three cohorts were found with generally higher concentrations in the Australian cohort followed by the early Danish cohort. Levels in the older Danish cohort were higher than in the recent one which is in agreement with regulations on phthalate use in the EU since 1999. Due to higher serum phthalate metabolite concentrations, detection rates of phthalate metabolites were higher in the Australian cohort compared to the Danish cohorts. Large inter-individual variations in serum phthalate metabolite levels were observed. In serum from all three cohorts, and urine from the most recent cohort, primary and secondary metabolites of di-(2-ethyl-hexyl) phthalate (DEHP) correlated

significantly while secondary metabolites of di-iso-nonyl phthalate (DiNP) only correlated in the older cohorts. In the Australian cohort, metabolites of di-n-butyl phthalate (DnBP) were also correlated. Secondary metabolites of DEHP in serum were positively correlated to urinary levels. Altogether, this indicates true exposure rather than post-collection contamination.

Conclusion: Serum samples are suitable to assess prenatal exposure to some phthalates. Geographical regions may differ in phthalate exposure patterns, and European regulations appear to have resulted in a decreasing exposure from the early 1990s to the 2010s in Denmark.

T5

Evaluation of Toll-like receptor 2 expression on T lymphocytes in patients with Graves' disease in relation to the clinical parameters

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Introduction: Graves'disease (GD) is a polygenic and multifactorial disease.

The innate immune system is a complex network of structured cells and proteins, including the Toll-like receptors (TLRs), which are also expressed on the cells of the adaptive immune system.

The Aim: Was to assess the relationship between the expression of TLR-2 on the surface of T CD4+ and CD8+ lymphocytes in patients with GD, and selected clinical and laboratory parameters.

Material and Methods: The study group consisted of 32 girls with newly diagnosed GD. The control group included 20 healthy girls. Peripheral blood (10 ml) was also taken from girls with GD after obtaining euthyreosis due to effective thyrostatic therapy. Immunophenotyping was performed using the flow cytometry method.

Results: The mean percentage of CD4+/ TLR-2+ T cells and CD8+/TLR-2+ T cells in the PB of patients with GD prior to treatment in comparison with the percentage of these lymphocytes in the control group was statistically significantly higher ($p<0.0001$). The mean percentage of CD4+/TLR-2+ T lymphocytes in the PB of patients with GD prior to treatment implementation was $1.32\pm0.59\%$. The average percentage of these cells in the group of healthy controls was $0.26\pm0.11\%$. After obtaining euthyreosis as a result of the treatment, the mean percentage of CD4+/TLR-2+ T cells in the PB of the studied group of patients with GD decreased to $0.59\pm0.09\%$ and this difference was statistically significant compared to the pre-treatment value ($p<0.0001$), but still remained higher than in the control group ($p=0.0003$). A statistically significant correlation was found between the expression of TLR-2 antigen on CD4+ T lymphocytes and serum FT3 concentration in patients with GD before treatment ($r=0.47$, $p=0.007$). The mean percentage of CD8+/TLR-2+ T cells in the PB of patients with GD prior to treatment implementation was $4.01\pm2.37\%$. The average percentage of these cells in the group of healthy people was

$1.30\pm1.46\%$. The mean percentage of CD8+/TLR-2+ T cells in the PB of the studied group of patients with GD before treatment compared to the percentage of these cells in patients with GD after obtaining euthyreosis ($2.35\pm1.27\%$) was statistically significantly higher ($p=0.0163$). After obtaining euthyreosis no statistically significant differences were found between patients with GD and control group.

Conclusion: Toll-like receptor 2 is expressed on significant percentage of T lymphocytes in patients with Graves' disease and is associated with the clinical response to treatment.

T6

Obesity in pediatric age: The analysis of genomic rearrangements

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Childhood obesity became a global plague: 9% of Italian children (17% of USA children) is obese and 21% is overweight. Nowadays only a small number of obese children undergoes genetic analysis, usually when obesity is associated with dysmorphic features. Our purpose was to identify genomic rearrangement causing obesity: we analyzed the DNA of 52 children by array-CGH (platform CytoScan-HD, Affymetrix). Patients included in our study were 29 males (55,8%) and 23 females (44,2%) obese, they presented dysmorphic features and/or mental retardation, hyperphagia and the improvement of the nutritional approach was not having any benefit reducing their weight. The average BMI was 28.42 kg/m^2 (SDS 2.64). 24 patients (46,15%) resulted positive on array-CGH analysis (33,4% females, 66,6% males); among these patients 41,2% presented dysmorphic features and 50% were affected by mental retardation. In 8 patients with a genetic rearrangement this was related to obesity and in 1 patient the link was suspected but not proved. Genetic rearrangements identified that can be causative of obesity are 4 deletions and 4 duplications. Del16p11.2 (813kb e 232kb) are described in association with obesity in childhood; dupXp22.31(1,6Mb) (genes HDHD1, STS, VCX, PNPLA4) causes over-expression of PNPLA4, that has been related to obesity. Genetic rearrangements of single genes are two dup18q(393 kb) and one del7q21.3(55kb), involving respectively genes ONECUT2 and BAIAP2L1, coding for molecules part of insulin pattern signaling. Dup3q24q25.1(180kb) and del20q13.13(109kb) code for CP and STAUI1: among obese patients have been described mutations of these two genes but their pathogenetic role has not be clarified yet. Del6q21(33kb) involves gene LAMA4: this rearrangement has an undefined meaning; in animal models LAMA4 seems to have a function in development of fatty tissue but in humans this function is not known yet. 46,15 % of patients of our cohort presented array-CGH positive for genomic rearrangements and this data justifies the execution of genetic analysis in obese children presenting dysmorphic features and/or mental retardation. 33,3% of our patients resulted positive on array-CGH analysis in absence of dysmorphic

features and/or mental retardation, so genomic analysis could have an important role either in obese patients without syndromic features. We can affirm that in obese children array-CGH analysis could help in identification of causative genetic mutations, with consequent advantage in therapeutic management and follow-up of these patients.

T7**Establishing of a novel NGS tool for the diagnosis of X-linked hypophosphatemia (XLH)**

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X-linked hypophosphatemia (XLH) is the most common genetic disorder of phosphate homeostasis. It is caused by inactivating mutations in the *PHEX* gene, which encodes a phosphate regulating endopeptidase predominantly expressed in osteoblasts, osteocytes, and odontoblasts.

In children there is a broad phenotypic spectrum of XLH ranging from isolated hypophosphatemia without clinical signs up to severe symptoms, such as rickets, extreme lower limb deformities, distinct tooth problems, and a disproportionate short stature. In adults suffering from XLH further symptoms occur, such as osteomalacia, arthritis, pseudo fractures, and low final height.

Since XLH is a rare disease, the diagnosis is frequently delayed, which has a significant impact on patient outcomes. In the past, molecular genetic testing included single exon/gene testing by Sanger sequencing analysis, which has been expensive and very time-consuming because of the largeness of the *PHEX* gene, including twenty-two exons.

A new NGS panel tool was designed, investigating not only *PHEX*, but also ten other genes, being candidate genes for other phosphate wasting disorders. For validation of the panel we involved fifty-two DNA samples from patients that had been sent to the University of Luebeck, Germany, for molecular genetic testing from December 2007 until today. All patients had the clinical and/or biochemical diagnosis of XLH and all (but three) had a proven molecular genetic change in *PHEX* revealed by Sanger sequencing in our laboratory. We included the samples of thirty-one females and twenty-one males of unrelated individuals, ranging from two years and ten months until forty-five years and nine months of age at the time of diagnosis.

The DNA samples were sent anonymous and blinded to our partner company "Bioglobe". The new developed NGS tool revealed in all patient samples with known changes in *PHEX* alterations, including different missense-, nonsense- and frameshift mutations, one splice site mutation, and in addition a duplication and a deletion. The molecular changes were spread over the whole gene. By using the new NGS tool, we confirmed in all cases the formerly made molecular diagnosis. The coverage of the *PHEX* gene was about 100%.

This new panel will be not only a valuable tool for a reliable and faster diagnosis of XLH, but also for other disorders of renal

phosphate wasting having a similar phenotype, but a different molecular genetic change in one of the other candidate genes.

T8**Bone mineral density (BMD) in women with Turner syndrome (TS) from the DSD-LIFE cohort, an epidemiological study**

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Aim: The objective of the study was to determine bone mineralisation density in Turner syndrome (TS) from DSD life cohort, and to analyse the trabecular (lumbar spine = LS) and cortical bone (femoral neck = FN) mineralisation.

Materials and Methods: This study was part of the DSD-LIFE study, a cross-sectional clinical outcome study of the BMD of TS adult patients from paediatric cohorts. BMD of the LS and FN were expressed in g/cm² and in women's T scores. Osteoporosis was defined for T score < -2.5 and osteopenia between -1 and -2.5 T score.

Results: In the DSD-LIFE cohort, 113 patients with TS had data of BMD in 4 European countries (Germany n= 34, Netherlands n=41, Poland n=3 and France n=39). History of fracture was found for 8.3% patients. 10.9% of the cohort presented osteoporosis.

Mean age was 30.15 ± 11.1 years. Mean height was 152.4 ± 6.9 cm, mean weight was 59.1 ± 13.6 kg and mean BMI was 25.5 ± 5.6 kg/m². Mean gynaecological age (GA) (number of years after menarche) was 14.7 ± 10 years with a mean age of puberty induction at 14 years ± 3 years.

The median for BMD of FN was 0.84g/cm² (IQR 0.75 ; 0.92 g/cm²) with T score of -0.7 SD (IQR -1.5 ; -0.2 SD). The median for BMD of LS was 1.0 g/cm² (IQR 0.93 ; 1.09g/cm²) with T score of -0.6 SD (IQR -1.4 ; -0.1 SD). No difference was noted according to karyotype (45X n=58, and no monosomy n=59). No difference was noted according to induction (n=55) or spontaneous puberty (n=26) and according the hormonal treatment. DMO decrease significantly with age and with GA for the FN ($r=-0.2181$, $p=0.0450$) but not for LS. DMO (FN or LS) was not significantly different between the group of woman under 150 cm and the group of woman above 150 cm.

Conclusion: The data of this study report a positive efficiency of estrogenic substitution on bone in TS adult and highlights the need to encourage hormonal treatment compliance for those patients.

T9**Empagliflozin And GABA Improve β -Cell Mass And Glucose Tolerance In New-Onset Type 1 Diabetes**

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Presently, the autoimmune character of T1D is challenged, but it is indisputable that inflammation plays a key role in its development. We hypothesized that glucotoxicity could contribute to β -cell mass destruction through maintenance of inflammation. Here, we aimed to evaluate, after diabetes onset, the potential of empagliflozin (EMPA) to protect β -cell mass against glucotoxicity, in monotherapy or in association with GABA, tested for its potential to increase residual β -cell mass. In a streptozotocin-based mouse model of T1D, empagliflozin and/or GABA were delivered by oral gavage or intraperitoneal injection, respectively, during seven days or three weeks. As shown by glucose tolerance test, EMPA-treated T1D mice had a better glucose homeostasis as compared to untreated T1D mice (236.9 ± 28.4 vs 454.4 ± 30.5 mg/dL). Furthermore, FFA level was decreased in EMPA-treated T1D mice compared to untreated T1D mice (0.7 ± 0.1 vs 1.5 ± 0.2 mmol/L). EMPA-treated T1D mice had a better islet density, numbers and preservation of islet architecture, compared to T1D mice. T1D mice showed islet with immune infiltration whereas EMPA-treated T1D mice displayed no islet infiltrate (0 ± 0 vs $21 \pm 13\%$). Islets from EMPA-treated mice were also less subjected to ER stress and inflammation, as shown by qPCR analysis. Furthermore, parameters of glucose homeostasis and β -cell mass were also improved, as compared to diabetic controls, when T1D mice were treated for 3 weeks with GABA and EMPA. Interestingly, T1D EMPA+GABA mice had higher glucagon levels than T1D mice (79.4 ± 26.5 vs 161.44 ± 5.2 pg/mL), without modifications of glucagon area/islet area ratios (28.8 ± 4.3 vs $33.0 \pm 4.4\%$). Empagliflozin and GABA, used in monotherapy, have positive effects on β -cell mass preservation or proliferation through an indirect effect on islet cell inflammation and ER stress. Further research is mandatory to evaluate whether empagliflozin and GABA may be a potential therapeutic treatment to protect β -cell mass after T1D diagnosis.

T10**Changes in adrenal androgens and steroidogenic enzyme activities in children aged 2, 4, and 6 years: Steroid hormone profiling from the prospective cohort study**

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Introduction: Adrenarche refers to the increase in adrenal androgen synthesis. However, process of adrenal androgen production in early childhood remains to be elucidated. The aim of this study was to evaluate changes in adrenal androgen levels and steroidogenic enzyme activities associated with adrenarche using a prospective cohort.

Methods: A total of 229 children (124 boys, 52.4%), who had participated in the Environment and Development of Children (EDC) cohort at age 2, 4, and 6 years old were enrolled. Anthropometric data at each visit and birth data were collected. Steroid profiles were analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS). A total of 10 adrenal hormones were measured including dehydroepiandrosterone (DHEA), DHEA sulfate (DHEA-S), 17-hydroxyprogesterone, androstenedione, testosterone, pregnenolone sulfate, cholesterol sulfate, testosterone, progesterone, 17-hydroxypregnolone, and pregnenolone. Steroidogenic enzyme activities were calculated using precursor/product ratios, such as 17α -hydroxylase, 17,20-lyase, 3β -hydroxysteroid dehydrogenase (HSD), 17β -HSD, and DHEA sulfotransferase. Steroid levels and enzyme activities were compared according to age and sex. Biochemical adrenarche was defined as a DHEA-S concentration of 188.1 ng/mL using LC-MS/MS. Factors affecting increasing levels of DHEA-S were analyzed.

Results: Data for 200 subjects (114 boys, 57.0%) with all steroid profiling results at 2, 4, and 6 years were analyzed. DHEA, DHEA-S, and androstenedione increased between 2 and 4 years in both sexes. DHEA and androstenedione were higher in girls than in boys at the age of 6 years. DHEA sulfotransferase activity increased between 2 and 4 years in both sexes. Between 4 and 6 years, activities of 17α -hydroxylase and 17,20-lyase increased, although 3β -HSD and 17β -HSD activities decreased. In girls, 17,20-lyase activity was higher and 3β -HSD and 17β -HSD activities were lower than in boys. Factors associated with increasing DHEA-S concentration over visits were age and body mass index. DHEA-S levels at the age of 6 years were significantly associated with being born small for gestational age and bone age on the third

visit. Biochemical adrenarche was observed in 27 children (13.5%) with no sex difference.

Conclusions: Adrenal androgens began to increase between the ages 2 to 4 years. Increased activity of DHEA sulfotransferase began between 2 and 4 years. Changes in steroidogenic enzyme activity to increase DHEA-S concentrations started between 4 and 6 years with increased 17,20-lyase and decreased 3 β -HSD activity. A longitudinal study with samples at the age of 8 years would be needed.

T11

Droplet Digital PCR Techniques to detect R201 mutations in the Mccune-Albright Syndrome

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Background: MAS is a rare disorder, this syndrome is classically characterized by a triad of physical signs: cafe-au-lait skin pigmentation(SP), fibrous bone dysplasia(FD), peripheral precocious puberty(PPP). In children, the most frequent initial presentation of MAS is PPP. MAS is caused by postzygotic activating mutations at the R201 codon of the GNAS gene, leading to a state of somatic mosaicism. In MAS patients, the frequency of mutations is expected to be generally low in clinically unaffected tissues such as peripheral blood leukocytes (PBL). Our aim to improve the mutation detection rate and quantify the presence of R201 GNAS mutations in PBL of MAS patients.

Methods: Compared with the PAP results, ddPCR techniques was used to search for R201 mutations in the DNA of blood from 73 MAS patients and 30 controls. The ability of ddPCR to provide quantitative data was tested in the dilution of wild -type, R201H,R201C cloned peripheral blood leukocytes.

Result: Compared with the PAP results, ddPCR showed that the analysis results of GNAS gene were obviously superior to the PAP method, especially for the non classic MAS, which was very difficult to be diagnosed clinically (77% and 9%), while the two generation sequencing could get a higher positive rate after the sequence of sequencing.

Conclusion: ddPCR techniques to the clinical screening of MAS molecular defects for the first time, and its efficiency is far higher than that of ordinary PCR. ddPCR is close to the classic and non classical positive rate of 70%, so it is currently in MAS.

T12

The first description of large pathogenic deletion in ACAN gene and additional cases with novel pathogenic ACAN variants

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Introduction: Recently novel approaches, through implementation of next-generation sequencing (NGS) in clinical practice for genetic evaluation of idiopathic short stature, has permitted to identify new variants of genes which modulate function of growth plate, including heterozygous mutations of the aggrecan gene. Aggrecan, a large chondroitin sulfated proteoglycan, is a major structural component of the extracellular matrix of cartilage, including growth plate, articular and intervertebral disc cartilage. We herein report five novel pathogenic variants in ACAN gene detected in five unrelated families using next-generation sequencing. Furthermore, we present the first large exonic deletion in ACAN gene in additional family, detected with array comparative genome hybridization (aCGH). Our study further expands clinical spectrum of ACAN phenotype.

Methods: Our baseline group comprised 50 children and adolescents with one inclusion criteria, i.e. height bellow -2 standard deviation scores (SDS) and five exclusion criteria: (i) growth hormone (GH) deficiency, (ii) hypothyroidism, (iii) chronic illness, (iv) defined skeletal dysplasia and/or syndrome, (v) cytogenetically detectable chromosomal abnormalities (e.g. Turner syndrome). From the baseline group we then formed a study subgroup of 16 individuals with advanced bone age and/or autosomal dominant inheritance pattern of short stature. We performed targeted or next-generation sequencing. Depending on the selection criteria (i.e., familial short stature and advanced bone age), additional array comparative genomic hybridization (aCGH) was performed.

Results: We identified 5 novel heterozygous ACAN mutations (c.301C>T, c.410_418delinsTGGA, c.2099G>A, c.7041delG, c.7069A>T) and first large exonic deletion in ACAN gene (15q26.1(89383692_89386488)x1)). Reported variants cosegregated with severe short stature phenotype in probands' respective families, except in one family member who had unexpected growth pattern with normal height (+0.1 SDS). The prevalence of ACAN defect in our study cohort is estimated to be 37.5% (6/16).

Conclusion: Our results indicate good inclusion selection criteria with high yield of ACAN positive probands. Based on our first description of the large pathogenic deletion in ACAN gene, we propose new diagnostic algorithm for aggrenopathies with inclusion genetic analysis for possible coding indels (ie., aCGH, MLPA) of ACAN gene.

T13**Results from the implementation of a 2 year growth awareness and growth disorders screening campaign (GrowInform)**

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Aim: Evaluation of the results from the campaign GrowInform (2017-2019), a project with the main aim to raise awareness of growth disorders, and secondary aims to facilitate screening for growth deviations in children from areas with no easy access to pediatric endocrinologists, thus achieving earlier diagnosis and treatment.

Methods: For 2 years (April 2017 to March 2018), GrowInform acted in 13 cities and towns from Eastern and Central Bulgaria (565,531 children 1 to 19 years). To increase participation rate, GrowInform worked in partnership with more than 100 media channels and social networks (Facebook, www.growinform.org, radio, television, Internet sites, newspapers, etc.). With the help of a PR specialist, interviews and publications with information about the visits in targeted areas were distributed. Outreach clinics were organised with simultaneous dedicated symposia and public lectures. The identified children with growth disorders were referred for further evaluation to the nearest pediatric endocrinologist/tertiary clinic.

Results: The vast majority of patients received information for GrowInform campaign from Facebook (36.29%), followed by Internet based media (27.01%) and General Practitioners' referrals (12.65%). Radio/TV channels (12.24%) and peer referrals (11.81%) were less presented.

A total of 237 children were consulted at a mean age 6.7 ± 4.2 years; 97 (40.9%) children were directed for further evaluation. A total of 69 (29.1%) children were fully assessed and their diagnosis finalised; 22 (9.3%) of them commenced GH therapy; 47 (19.8%) are still followed up or the tests are pending. Further 4 children with Prader-Willi syndrome were diagnosed at neonatology clinics after a dedicated symposium at a national meeting and commenced GH treatment at the age of 5.7 ± 5.7 (11 months to 12.5 years).

GrowInform created friendly and positive media environment and the general number of growth referrals increased. In 2017, 13 children who started GH treatment were 12.5% of all treated; in 2018 the new patients were 37, 29.4% of all treated. The age at start of therapy decreased from 8.7 ± 5.8 years in 2016 to 7.3 ± 3.3 in 2018. Children with rare syndromes received definitive diagnosis and treatment (3 children with Silver-Russell syndrome, 5 with Prader-Willi syndrome, 3 with Turner syndrome, one 45X0/46XY boy, 2 with Noonan and 1 with Leopard syndrome, a pseudohypoparathyroidism family, etc.).

Conclusion: GrowInform campaign was an effective tool to improve growth deviations diagnosis and treatment. To prolong the campaign effect, a strategy for publication of educational and growth patient material is under development.

T14**The Effect of Endocrine Disrupting Chemicals to Precocious Puberty in Children with Exposure History of 'Slim'**

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Background: Recently, the puberty is becoming to start earlier. This early beginning of the puberty is multifactorially related to genes, hormones and environmental factors. It has been already known in many animal experiments that endocrine disrupting chemicals (ECDs) are deeply involved in regulation of endocrine systems. However, clinical studies in humans are limited. Recently, the toy of 'Slim' which thought to contain ECDs such as phthalates is very popular in primary school children. This study was done to see the effect of ECDs in primary school children's puberty.

Materials & Methods: Study patients consisted of 140 children whom GnRH stimulation tests were done due to precocious puberty between Jan 2018 and Dec 2018. Twenty-seven boys (19%) and 113 girls (81%) were enrolled. Precocious puberty was defined when the first pubertal sign began below the age of 8 yrs in girls and 9 yrs in boys along with the advanced bone age ≥ 1 yr. GnRH stimulation tests were performed in all study patients. Study patients were classified into two groups; 'GnRH+ group' (peak LH ≥ 5 mU/mL) and 'GnRH- group' (peak LH < 5 mU/mL). The exposure history of ECDs was accepted when study patients play with 'Slim' ≥ 3 times/week for ≥ 6 months at the time of GnRH stimulation tests. BMI, changes of bone-age, auxological data and various laboratory data were retrospectively analyzed.

Results: Fifty-eight (41%) were enrolled in 'GnRH+ group', and 82 (59%) in 'GnRH- group'. Seventy-nine out of 140 (56%) showed a significant exposure history of ECDs; 14/58 (24.1%) in 'GnRH+ group' and 65/82 (79.2%) in 'GnRH- group'. A significant exposure history of ECDs was statistically higher in 'GnRH- group' compared to 'GnRH+ group' ($p < 0.05$). The possibility of GnRHa treatment was 5.55 times higher in patients with significant exposure Hx of ECDs compared to without significant exposure Hx of ECDs ($p < 0.001$). Bone-age advancement was also higher in patients with significant exposure Hx of ECDs compared to without significant exposure Hx of ECDs ($p < 0.05$).

Conclusion: It can be said that the exposure of ECDs seems to be related to the early pubertal onset and rapid bone-age advancement. Further study is necessary.

T15**Intestinal microbiota development differs between pubertal boys and girls**

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Introduction: The human fecal microbiota is known to shift in composition during adolescence, but whether fecal microbiota is associated with timing of sexual maturation is unknown. In mice, the change in the composition of fecal microbiota during puberty appears to be sex-specific and associate with changes in testosterone. We investigated the association between intestinal microbiota and pubertal timing in adolescents.

Subjects and Methods: The study is an allergy-prevention-trial cohort including 415 participants with high risk for allergy. The subjects randomly received a mixture of four probiotics with prebiotic, or placebo, for the first six months of life. The treatment did not affect growth.

At the 13-year-follow-up, participants provided a fecal sample, and their growth data were analysed. Microbiota composition of the fecal samples was analysed by 16S rRNA amplicon sequencing. Samples with less than 900 reads were excluded.

We modelled height progression with a polynomial function and produced individual growth velocity curves for each participant. We identified *age at peak height velocity* (APHV), a marker of puberty timing, using the derivative of the growth velocity curve. We calculated *time from peak height velocity* (TPHV), a marker of pubertal maturation by subtracting age at fecal sampling from age at peak height velocity. We used $p < 0.001$ as a cut-off point, and limited the analysis on bacterial genera. The statistical analysis was carried out with R using the mare-package. The analysis was adjusted for relevant confounders.

Results: Sufficient growth data for assessment of puberty timing was available from 35% of the 415 participants (60% females, 40% males). One girl and 16 boys were prepubertal (self-reported Tanner staging). Among boys, TPHV was negatively correlated with relative abundance of *Burkholderia* ($\beta = -1.549$). Ignoring the samples with zero-observations, TPHV was negatively correlated with the abundance of *Actinomyces* ($\beta = -1.091$). Among girls, TPHV was positively correlated with the abundance of *Gemella* ($\beta = 0.573$) and negatively with *Barnesiella* ($\beta = -0.145$) and *Oscillospira* ($\beta = -0.493$). Ignoring samples with the zero-observations, TPHV was also positively correlated with the abundance of *An-aerospora* ($\beta = 0.350$) and *Solobacterium* ($\beta = 0.337$) and negatively with the abundance of *Megamonas* ($\beta = -1.789$).

Results for APHV were very similar to those with TPHV.

Conclusion: We conclude that the timing of human puberty is correlated with fecal microbiome in a sex-specific manner.

Raivio and Kuitunen contributed equally to this work.

T16**IGF2 Mutations: Report of Six Japanese Cases and Phenotypic Comparison with H19/IGF2:IG-DMR Epimutations including literature cases**

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Object: IGF2 is a paternally expressed gene involved in the development of Silver-Russell syndrome (SRS). Here, we report six Japanese patients with IGF2 mutations and compare clinical findings between patients with IGF2 mutations including literature cases and those with H19/IGF2:IG-DMR epimutations.

Patients: We recruited six Japanese patients with IGF2 mutations. The major reason for molecular studies was Ectrodactyly, fetal growth restriction (FGR) and disorder of sex development (DSD) in case 1, multiple congenital anomalies/mental retardation (MCA/MR) in case 2, SRS and DSD in case 3, SRS in case 4, ectrodactyly and FGR in case 5, and FGR and extremely high serum IGF-I value in case 6.

Molecular Studies: We first performed [1] pyrosequencing-based methylation analysis for SRS-related DMRs in cases 3 and 4, [2] standard Sanger direct sequencing for *IGF1* and *IGF1R* in case 6, and [3] array comparative genomic hybridization analysis to examine pathogenic copy-number variants in cases 1–6, using leukocyte genomic DNA samples. However, no genetic or epigenetic abnormality was identified. Thus, we carried out comprehensive mutation analyses with TruSight One Sequencing Kit, a custom-made HaloPlex Target Enrichment System, and whole exome sequencing.

Results: We identified various *IGF2* mutations, *i.e.*, case 1 with a frameshift mutation p.(Leu37Glnfs*31), case 2 with a splice site mutation (c.-6-1G>C) leading to skipping of exon 2, and cases 3–6 with different missense mutations (p.(Cys70Tyr), p.(Cys71Arg), p.(Cys33Ser), and p.(Cys45Ser)) affecting cysteine residues involved in the S-S bindings. All the mutations resided on the paternally inherited allele, and the mutation of case 6 was present in a mosaic condition. Phenotypic comparison between apparently non-mosaic patients with *IGF2* mutations identified to date and multiple patients with H19/IGF2:IG-DMR epimutations revealed that, while overall phenotype was similar between the two groups, *IGF2* mutations resulted in SRS with high Netchine-Harbison score ($\geq 5/6$), low frequency of hemihypoplasia, high frequency of feeding difficulty and/or reduced body mass index, and mild degree of relative macrocephaly, together with occasional development of severe limb malformations, high frequency of cardiovascular anomalies and developmental delay, and low serum IGF-II values.

Conclusion: The results are primarily explained by the *H19/IGF2*:DMR methylation pattern-dependent paternal *IGF2* expression in most tissues and the tissue-specific promoter-dependent biparental *IGF2* expression in the brain and liver, and by the mosaic condition of *H19/IGF2*:DMR epimutations and the non-mosaic condition of *IGF2* mutations. The present study indicates that *IGF2* mutations are associated with characteristic clinical features.

T17

Factors Associated with Dyslipidemia in Patients with Type 1 Diabetes: A Single-Center Experience

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Background: Type 1 diabetes (T1D) contributes to altered lipid profiles and increased cardiovascular disease (CVD) risk. Youth with T1D may have subclinical CVD within the first decade of diagnosis.

Objective: To assess risk factors associated with dyslipidemia in young subjects with T1D.

Study Design and Methods: A longitudinal and cross-sectional retrospective cohort study was conducted based on data collected from medical records of T1D patients treated in the National Center for Childhood Diabetes in Israel. Clinical and laboratory parameters including lipid profile [total cholesterol (TC), triglycerides, low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C)] were extracted from patient's computerized medical records. A structured telephone interview was conducted to update the family history for cardiometabolic diseases (T2D, CVD, hypertension, dyslipidemia). Potential risk factors and confounders for 10-year outcomes of lipid profiles were analyzed by stepwise linear regression models. Potential risk factors included were gender, ethnicity, Tanner stage, BMI-SDS, systolic and diastolic blood pressure (BP), and glycosylated hemoglobin (HbA1c) levels, age at diagnosis and T1D duration, and family history of cardiometabolic diseases.

Results: 170 young subjects with T1D (86 males; mean age 12.2 ± 4.6 years and HbA1c 8.2 ± 1.4% at baseline) were followed from diabetes onset through young adulthood. Significant risk factors for elevated TC: diastolic BP [B(SE)=17.9(6.0), P=.004], HbA1c [B(SE)=6.5(3.0), P=.033], family history of CVD [B(SE)=14.1(6.5), P=.033], female sex [B(SE)=11.4(5.3), P=.036]; elevated LDL-C: diastolic BP [B(SE)=14.3(5.1), P=.007] and family history of CVD [B (SE)=11.5(5.6), P=.044]; elevated triglycerides: HbA1c

[B(SE)=16.1(5.5), P=.004] and diastolic BP [B(SE)=23.4(10.9), P=.035]. No predictors were found for low HDL-C levels.

Conclusions: Our findings suggest that elevated lipid levels are associated with glycemic control, diastolic BP, positive family history of CVD, and female sex. Since poor glycemic control and elevated BP aggravate the risk for dyslipidemia, careful surveillance is warranted to prevent and control these modifiable risk factors already from childhood and adolescence. The more prominent clustering of CVD risk factors in poorly controlled T1D patients underscores the importance of a more vigorous intervention in this group.

T18

Early treatment with intravenous bisphosphonates prevents severe postnatal bone loss in children with Osteogenesis imperfecta

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Objective: Osteogenesis imperfecta is an inherited disorder characterised by bone fragility. Antiresorptive treatment with bisphosphonates is a well-established first line medical treatment in OI types III/IV. Nevertheless, there is no consensus on treatment modalities, like which bisphosphonate to use in which dose and when to initiate treatment. The objective of this work was to evaluate the therapeutic effect of a one-year treatment period with bisphosphonates (neridronate i.v., 2mg/kg body weight every 3 months) on vertebral shape, bone mineral density and mobility in infants with severe OI, depending on the onset of treatment.

Methods: We analysed twelve infants with OI type III or IV receiving bisphosphonates (neridronate) within the first 6 month of life and subanalysed the results in respect of the time of treatment initiation. Areal Bone mineral density (BMD) of the lumbar spine (L2-L4) was assessed via DXA (GE Lunar iDXA). Vertebral shape was assessed by x-ray of the lateral spine (Morphometry COIN score). Mobility progress was analysed by age, when children reached certain defined motor milestones, based on parent's questionnaires.

For subanalysis we set up matched pairs, to control for severity: early initiation, meaning age of first bisphosphonate treatment within the first month of life and late initiation, meaning age of first bisphosphonate treatment at 3.8 +/- 1.7 months.

Results: All patients presented with a reduced mean lumbar spine aBMD at start of treatment and after one year (early initiation: 0.231 g/cm² vs 0.244 g/cm² (Z-score - 1,4 SD vs. -2,9 SD); late initiation 0.131 g/cm² vs. 0.236 g/cm² (Z-score -7,76 SD vs. -3,2 SD)). Vertebral morphometry score changed from 1 to 24.8 in the early treatment group and from 57.25 to 53.8 in patients which

started later with treatment. Motor function assessment revealed “turning head” was reached within 1,1 months vs. 2 months and “first supported steps” within 17.0 vs 22.5 months.

Conclusion: OI patients starting intravenous neridronate within the first month of life showed less postnatal bone loss. Early treatment seems to preserve the prenatally gained bone mass. We found less deterioration of vertebral shape in patients started early. Those patients also tended to reach motor milestones earlier, than children starting at the mean age of 3.8 months. Therefore, one can assume that an early antiresorptive treatment might be beneficial for the development of the affected children.

T19

Urinary Gonadotrophins in Girls with Turner Syndrome

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Background: Girls with Turner Syndrome (TS) are at an increased risk of primary ovarian failure. Oestrogen replacement is commenced at around the age of 12 years, in girls who do not enter puberty spontaneously, with incremental changes to the dose over the next 3 years until adult replacement doses are achieved. We have previously shown good correlation between serum and urinary LH (uLH) and FSH (uFSH) in children being assessed for disorders of puberty.

Objectives:

1. To determine whether there was a correlation between serum and urinary LH and FSH in hypergonadotropic states;
2. To determine whether uFSH could similarly predict ovarian failure in TS as Anti-Müllerian Hormone (AMH).

Patients and Methods: A retrospective analysis of 37 TS girls attending the paediatric TS clinic in Glasgow between February 2015 and January 2019, in whom 96 non-timed spot urine samples were available with a median age at time of sample of 12.89 years (range 3.07-20.2 years). uLH and uFSH were measured by chemiluminescent microparticle immunoassay and corrected for urinary creatinine (uLHC_r and uFSHC_r). Simultaneous serum gonadotrophins and AMH were available in 30 and 26 girls, respectively. An AMH level <4 pmol/L was indicative of ovarian failure. Clinical information was collected from electronic case records and data were analysed using IBM SPSS ($P<0.05$).

Results: 48.6% had 45,X karyotype. 22/26 (84.6%) had started oestrogen replacement at a median age of 13.2 years (range 11.8-16.4 years). A strong correlation was found between serum LH and uLH ($r = 0.860$, $P<0.001$) and serum FSH and uFSH ($r = 0.905$, $P<0.001$). After correction for creatinine excretion the correlation remains significant, but the coefficient was smaller (uLHC_r $r = 0.537$, $P=0.002$ and uFSHC_r $r = 0.381$, $P=0.038$). Among patients ≥ 10 years

not on oestrogen replacement, ROC curve identified uFSH as a reasonable predictor for AMH <4 pmol/L: uFSH of >10.85 U/L predicts an AMH <4 pmol/L with 75% sensitivity and 100 % specificity (AUC 0.875). uFSH had similar ability to predict ovarian failure in girls with TS (AMH <4 pmol/L) as serum FSH (AUC 0.906).

Conclusion: uLH and uFSH are non-invasive, useful and reliable markers of ovarian insufficiency in hypergonadotropic states as TS. uFSH could provide an alternative to AMH (in centres which are limited by availability or cost) in predicting ovarian failure and the requirement for oestrogen replacement in pubertal induction.

T20

Molecular and phenotypic spectrum of Noonan syndrome in Chinese patients

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Background: Noonan syndrome (NS) is a common autosomal dominant/recessive disorder. No large-scale study has been conducted on NS in China, which is the most populous country in the world.

Methods: Next-generation sequencing (NGS) was used to identify pathogenic variants in patients that exhibited NS-related phenotypes. We assessed the facial features and clinical manifestations of patients with pathogenic or likely pathogenic variants in the RAS-MAPK signaling pathway. Gene-related Chinese NS facial features were described using artificial intelligence (AI).

Results: NGS identified pathogenic variants in 103 Chinese patients in eight NS-related genes: *PTPN11* (48.5%), *SOS1* (12.6%), *SHOC2* (11.7%), *KRAS* (9.71%), *RAF1* (7.77%), *RIT1* (6.8%), *CBL* (0.97%), *NRAS* (0.97%), and *LZTR1* (0.97%). Gene-related facial representations showed that each gene was associated with different facial details. Eight novel pathogenic variants were detected and clinical features due to specific genetic variants were reported, including hearing loss, cancer risk due to a *PTPN11* pathogenic variant, and ubiquitous abnormal intracranial structure due to *SHOC2* pathogenic variants.

Conclusion: NGS facilitates the diagnosis of NS, especially for patients with mild/moderate and atypical symptoms. Our study describes the genotypic and phenotypic spectra of NS in China, providing new insights into distinctive clinical features due to specific pathogenic variants.

Poster Category 1

Adrenals and HPA Axis

P1-1

Could a Glucocorticoid Receptor Polymorphism be Protective against Hypothalamic-Pituitary-Adrenal Axis Suppression in Asthmatic Children on Corticosteroids?

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Background: Homozygotes for the single nucleotide polymorphisms (SNPs) rs242941 and rs1876828 of the corticotrophin-releasing hormone receptor 1 (CRHR1) gene were previously associated with lower stimulated and basal cortisol levels respectively in asthmatic children on inhaled corticosteroids. Heterozygotes for rs41423247 of the glucocorticoid receptor (NR3C1) gene were found to have higher basal cortisol levels.

Objectives: To determine whether the SNPs rs242941 and rs1876828 of the CRHR1, and rs41423247 of the NR3C1 gene are associated with hypothalamic-pituitary-adrenal suppression (HPAS) in asthmatic school children on corticosteroids.

Methods: DNA was extracted from saliva obtained from 96 asthmatic children, 5.2-15.6 years old, treated with inhaled and nasal corticosteroids, who had previously undergone basal cortisol (C) and metyrapone testing. HPAS was diagnosed if C was <83 nmol/l or the post-metyrapone ACTH (PACTH) level <106 pg/ml. Thirty-six children were classified as suppressed. Non-suppressed children were sub-classified according to their PACTH into a middle (106-319 pg/ml) and a high (>319 pg/ml) ACTH response group, comprising 29 and 31 subjects respectively. TaqMan PCR assays were utilized for genotyping. ANOVA, linear, logistic and multinomial logistic regression analysis were performed.

Results: Only rs41423247 was associated with HPAS ($p = 0.005$). Mean difference of PACTH of the CC compared to GG genotype was 278.5 (19.5-537) pg/ml while the difference of GC compared to GG genotype was 143.5 (11.6-275.5) pg/ml; ($p=0.030$ and 0.032 respectively). The C allele of this SNP is less likely to be associated with HPAS (odds ratio [OR] = 0.38 [0.18-0.82]) and appears to be dominant (OR = 0.33 [0.13-0.83]). On linear regression, the effect was both additive ($b = 137.7$, SE = 42.7, $p = 0.002$) and dominant ($b = 162.0$, SE = 53.0, $p = 0.003$). Dominance was confirmed on logistic regression ($p = 0.032$).

Conclusions: rs41423247 (CC) of the NR3C1 gene was associated with higher PACTH levels and is less likely to be associated with HPAS.

P1-2

Software-assisted Analysis of the urinary Steroid Metabolome in treated children with classic Congenital Adrenal Hyperplasia

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Background: Treatment of children with classic congenital adrenal hyperplasia (CAH) is a difficult balance between hypercortisolism and hyperandrogenism. Biochemical monitoring of treatment is not well defined.

Objective: Retrospective software-assisted analysis of urinary steroid metabolome analysis obtained by gas chromatography-mass spectrometry (GC-MS) for treatment monitoring of children with CAH.

Methods: We evaluated 24-hour urinary steroid metabolome analyses of 63 prepubertal children aged 6.9 ± 1.5 years with classic CAH due to 21-hydroxylase deficiency treated with hydrocortisone (HC) and fludrocortisone. We divided the subjects into five distinctive groups by k-means clustering using MetaboAnalyst 3.0 software. Steroidal fingerprints and clinical data of patients in each cluster were analyzed.

Results: Five unique clusters were generated by invoking the k-means clustering algorithm. Cluster #1 (N=5 (8%)) showed over-treatment consisting of a combination of high urinary cortisol metabolites and low metabolites of androgens and 17-hydroxyprogesterone (17OHP). Cluster #2 (N=18 (29%)) revealed good disease control due to moderate cortisol metabolites and suppressed androgen and 17-hydroxyprogesterone (17OHP) metabolites. Cluster #3 (N=15; 24%) demonstrated under-treatment through a combination of low cortisol metabolites and very high metabolites of androgens and 17OHP. Cluster #4 (N=6 (10%)) and cluster #5 (N=19 (30%)) both revealed differently kinds of treatment failures. Cluster #4 revealed unsuppressed very high androgen- and 17OHP metabolites despite appropriate urinary cortisol metabolites. In cluster #5, metabolites of androgens and 17OHP were moderately elevated although cortisol metabolites were markedly increased.

Conclusion: Software-assisted analysis of urinary metabolomes helps to monitor treatment of children with CAH. This method allows classification in under-, over-, and adequate-treated children as well as in patients with treatment failure.

P1-3**Simplifying the interpretation of steroid metabolome data by a machine-learning approach**

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Background: Liquid chromatography-mass spectrometry (LC-MS) based panels of steroid hormones and their precursors offer a distinct pattern of steroid metabolome for various disorders of adrenal and gonadal steroidogenesis. However, it may not be easy to handle this high throughput data rapidly in clinical setting which requires expert opinion for correct interpretations. Analytical results of steroid paneling can be allied to automated review systems to simplify the complexity of data for disease-related interpretation.

Methods: We have implemented a machine-learning algorithm for a time-saving and experience-independent review and interpretation of analytical results. We have tested the performance of this algorithm using our archived data of quantitation of 16 steroid hormones and precursors by an LC-MS/MS based panel in 500 healthy controls and 427 treatment-naive children-with a disorder of adrenal steroidogenesis. This cohort included classic CYP21A2 (n=75), non-classic CYP21A2 (n=19), CYP11B1 (n=66), mutation-positive HSD3B2 (n=31), mutation-negative HSD3B2 (n=21), CYP11B2 (n=19), CYP17A1 (n=11), POR (n=7) deficiencies and non-CAH PAI (n=21). Due to the relatively low numbers of some of the conditions in the patient cohort, the number of samples in one class has outnumbered the other one. This imbalance has been overcome by utilizing data sampling and boosting algorithms, specifically Random Oversampling Boosting (RUSBoost).

Results: Dataset of 415 patients fed to the algorithm with 10-fold cross validation to prevent overfitting. For discrimination of patients from the healthy controls; the sensitivity and specificity of the RUSBoost algorithm was 97.7% and 92.6%, respectively. The differentiation of each disorder could be achieved with overall accuracy of up to 95% independent of age and sex.

Conclusion: Application of RUSBoost machine learning algorithm enables a rapid and standardized review of complicated plasma steroid paneling data, which can widely be used by clinicians to make correct diagnosis for disorders of steroidogenesis.

P1-4**The Steroidal Milieu in Amniotic Fluid of Mid-Gestation: A Targeted GC-MS Metabolomics Study**

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Intact steroid hormone biosynthesis is essential for growth and development of the human fetus and embryo. In the present study, gas chromatography-mass spectrometry was employed to characterize the steroidal milieu in amniotic fluid (n=65; male: female = 35: 30) of mid-gestation (median: 18.8th week, range: 16.0th – 24.6th week) by a comprehensive targeted steroid hormone metabolomics approach. The levels of 52 steroids including pregnenolone and 17-OH-pregnenolone metabolites, dehydroepiandrosterone (DHEA) and its metabolites, progesterone and 17-OH-progesterone metabolites, sex hormones as well as corticosterone and cortisol metabolites were measured. The dominating steroids were the group of pregnenolone and 17-OH-pregnenolone metabolites (mean ± SD: 138.0 ± 59.3 ng/mL), followed by the group of progesterone and 17-OH-progesterone metabolites (107.3 ± 44.3 ng/mL), and thereafter DHEA and its metabolites (97.1 ± 56.5 ng/mL). With respect to sex steroids, only testosterone showed a significantly higher value in male fetuses (p<0.0001) reflecting testicular endocrine activity. Furthermore, the hormonal constellation in amniotic fluid was not indicative of an active androgenic "back-door" pathway. Of all estrogen metabolites, estriol showed by far the highest concentrations (33.2 ± 26.1 ng/mL). Interestingly, cortisol metabolites were clearly present (59.6 ± 13.6 ng/mL) though fetal *de novo* synthesis of cortisol is assumed to start from gestational 28th week onwards. Tetrahydrocortisol (THE) levels are 4 times higher than tetrahydrocortisol (THF) levels. Our comprehensive characterization of the steroidal milieu in amniotic fluid of mid-gestation shows presence of all relevant classes of steroid hormones. The steroidal milieu in amniotic fluid mirrors the steroidome of the feto-placental unit. Our set of basic data lays the foundation for further studies characterizing various diseases affecting steroid metabolism.

P1-5**18 years of neonatal screening for congenital adrenal hyperplasia in North-Eastern Italy: recall rate reduction thanks to liquid chromatography-tandem mass spectrometry as second tier test**

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Background: In North-Eastern Italy, a newborn screening for congenital adrenal hyperplasia (CAH) has been taking place since 2001 to diagnose the classical form of 21-hydroxylase deficiency

(21-OHD). Thanks to the screening program based on 17-OHP levels in dried blood spots, early diagnosis of CAH is possible, allowing appropriate precocious treatment and reducing mortality rates. Unfortunately, a high false positive rate, especially in preterm, low-birth-weight and critically ill newborns, is described.

Aims: The aims of our study are to summarize the results of the newborn screening for CAH held in the last eighteen years in North-Eastern Italy and to evaluate the diagnostic utility of simultaneous determination of 17-OHP, cortisol, 11-deoxycortisol, delta 4-androstenedione and 21-deoxycortisol by liquid chromatography-tandem mass spectrometry (LC-MS/MS) as second tiers performed on the same blood spot.

Materials and Methods: Since 2001 dried blood spots from newborns have been screened with a time-resolved fluoroimmunoassay method (DELFIA) for 17-OHP determination. Over the years, the cutoff levels of 17OHP were adjusted according to gestational age. Since 2017, samples resulted above the cutoff have been immediately analyzed by LC-MS/MS in order to differentiate affected patients from false positive newborns.

Results: Since 2001, 786.302 newborns have been screened, with 34 diagnosis of classic form of 21-OHD and a total incidence of 1:23126. To date, we have no information about false negative cases (sensitivity of 100%). Over the years, adjustments of cutoff values for 17-OHP based on gestational age and, in particular, the use of LC-MS/MS, as a second-tier test for positive CAH screening significantly reduced the recall rate (RR). RR varied by a maximum value of 1.06 in 2009 to 0.85 in 2016 before LC-MS/MS, and reached the value of 0.45 in 2017 and of 0.17 in 2018 after the introduction of LC-MS/MS.

Conclusions: The screening for CAH proved to be useful in the neonatal diagnosis of classic form of 21-OHD, allowing a precocious and appropriate treatment, significantly reducing mortality as well. Moreover, the use of LC-MS/MS as a second tier test resulted in a useful tool to improve the positive predictive value of the screening program. LC-MS/MS is not suitable to replace the conventional method, but it is extremely useful as a second-tier test in particular in preterm, low-birth-weight and critically ill neonates, preventing unnecessary blood draws, medical evaluations and stress to families.

P1-6

Health status of children with Congenital Adrenal Hyperplasia due to 21-hydroxylase deficiency in the United Kingdom: results of a multi-centre cohort study

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Introduction: Congenital adrenal hyperplasia (CAH) is associated with long-term health problems. However, little is known about co-morbidities and their onset in children and young persons (CYP).

Objective: To establish the health status of CYP with CAH across the United Kingdom.

Methods: A multi-centre prospective study recruited 102 patients with 21-hydroxylase deficiency targeting CYP aged 8-18 years (54 females, 48 males, 13.0 ± 2.92 years) from 13 centres across the United Kingdom and 83 matched controls. Recruitment took place between September 2016 and March 2019. Demographic, clinical, and metabolic data were explored by descriptive statistics and analysis of variance.

Results: Most CAH patients were of White (72.5%) or South-east Asian (19.6%) ethnicity. Glucocorticoid treatment (hydrocortisone 94.1%, prednisolone 5.9%) exceeded 15mg/m²/day in 27% of patients. 84.3% of patients received 3-4 doses/day with a higher am dose (50-70% of total daily dose in 32% patients; 30-50% of total daily dose in 35%). Glucocorticoid doses (mg/m²/day, median with interquartile range) were significantly higher in boys (14 (11.8-15.6)) compared to girls (11 (8.1-14.2))(p=0.002). 75% of patients received fludrocortisone with a median dose 90(64-133) mg/m²/day. 34.3% of patients required admission for adrenal crisis after diagnosis (1-2 episodes for 87.1%). Advanced bone age (>1.5 years) was not different between girls (23%) and boys (20%). Delta-SDS for target height was 1.2±1.4 for children younger than 12 years and 0.3±1.6 for 12-18 year-olds. Comparing height-SDS,

patients younger than 12 years were taller ($p=0.02$) and patients aged 12-18 years shorter ($p=0.03$) than controls. Patient weight-SDS (0.87; 0.03-1.35) and body-mass-index-SDS (0.98; -0.04-1.94) were significantly higher than in controls, 27.7% of patients were overweight and 22.8% obese. Five patients had high blood pressure. Post-glucocorticoid dose androstenedione was normal in 32%, suppressed in 7%, and elevated in 50% of patients; 17-hydroxyprogesterone was within target range in 20%, suppressed in 19%, and increased in 43% of patients. Biochemistry indicated normal sodium in all patients, low potassium in 1 patient, mildly raised creatinine in 9.8%, abnormal high lipids in 9.8%, and normal fasting glucose in all patients. Associated behavioural and mental health problems were reported for 11.3% patients aged 12-18 years, similar to the general population.

Conclusion: Our findings suggest that children with CAH have increased prevalence of growth problems, excessive weight, and metabolic co-morbidities compared to controls. Improved standardised treatment and personalised strategies for the management and monitoring of CAH in childhood are required to improve long-term patient outcomes.

P1-7

Influence of Internal Standards Choice on Quantification of 17 α -hydroxyprogesterone (17OHP) Using Mass Spectrometric Based Methods

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Objective: This project aims to evaluate the effect of two isotopically labelled internal standards on the quantification of 17OHP by liquid chromatography-tandem mass spectrometry (LC-MS/MS) and gas chromatography-tandem mass spectrometry (GC-MS/MS) as an orthogonal technique.

Methods: Three LC-MS/MS and one GC-MS/MS laboratories, spanning four countries worldwide, who routinely measure serum 17OHP, compared two internal standards as part of their patient runs. The only change to the respective laboratory standard operating procedure was the substitution of their internal standard (if different to in-house method) with: 1) IsoSciences carbon-13 labelled 17OHP-[2,3,4-¹³C₃]; and 2) IsoSciences deu-

terated 17OHP-[2,2,4,6,6,21,21-D₈]. Statistical interpretation of the data is based on the slope from the Passing Bablok regression, difference from the Bland Altman plots and the Student two tailed paired t-test, with confidence intervals (CI) of 95% and level of significance $p<0.05$ applied.

Results: The three LC-MS/MS and one GC-MS/MS laboratories successfully evaluated the two internal standards against altogether 232 patient samples. Analysis of the ¹³C- and D-labelled internal standard results from the individual laboratories, along with the combined all laboratory data, demonstrated agreement: the Passing-Bablok regression slope to include one in the CI; and Bland Altman difference to include zero in the CI. The all laboratory data t-test demonstrated a $p>0.05$.

Conclusions: Overall, the comparison between the results of ¹³C- and D-labelled internal standards for 17OHP showed not influence by the internal standard used.

P1-8

Follow-up and Prevalence of Precocious Puberty in Children with Classical Congenital Adrenal Hyperplasia diagnosed by Neonatal Screening

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Introduction: In children with classical congenital adrenal hyperplasia (CCAH) linear growth allows monitoring metabolic control. Precocious puberty could compromise their growth. There are few studies in patients with CCAH diagnosed by neonatal screening (NS) about this subject.

Aims: To analyze linear growth and precocious puberty in children with CCAH detected by NS.

Method: Thirty-two patients (F:15, M:17) with CCAH diagnosed by extracted 17OHP and molecular analysis were included. They were evaluated at start of treatment, 12 months of age, and then annually. Twenty one (F:9; M:12) of them started puberty and seven reached final height. We analyzed chronological age (CA) at start of treatment (CAST), z-height, z-BMI, hydrocortisone dose (HCd), bone age (BA) by Greulich and Pyle. We calculated Δ BA at start of puberty and one year previous; Δ BA-CA at start of puberty. Final height was compared with mid parental height (MPH). Statistical analysis: Anova test-Spearman correlation.

Results: Median CAST was 18(10;22) days.

No significant differences were found between variables analyzed by sex. Negative correlation was found between HCd and height ($r=-0.27, p<0.0001$). During follow-up, 21 patients started puberty, 9 boys and 4 girls at 11 ± 0.9 and 9.5 ± 0.21 years, respectively. Final height in seven of them (F:2; M:5) was -1.17 ± 0.6 SDS, -0.75 ± 0.79 SDS below MPH. Six boys and five girls (34%) presented precocious puberty at 6.4 ± 1.85 and 6.72 ± 0.35 years, respectively. Δ BA at start of puberty and one year previous was +3.05 years in boys and +1.8 years in girls. Δ BA-CA at start of puberty was +4.4 years in boys and +3.5 years in girls. They are in treatment with GnRH analogue and haven't reached final height yet.

	Start	1st year	2nd year	3rd year	4th year	5th year
Mean height SDS	-0,9±1,5	-1,6±1,67	-1,15±1,27	0,71±1,13	0,47±1,23	0,11±1,28
Mean BMI SDS	-1,46±1,21	0,67±1,42	0,68±0,91	0,89±0,96	0,97±1,23	1,33±1,4
HCd (mg/m2/day)	36 (32,8;43,55)	17,94 (16,12;19,52)	16 (14,44;19,2)	15,13 (13;19,91)	14,52 (11,83;16,83)	14 (10,79;18,09)
Mean BA SDS		0,87±0,33	1,89±0,85	2,59±1,03	3,88±1,33	5,36±2,43

Conclusions: All patients showed normal BA up to the age of 5 years, but later on, BA progressed rapidly in patients who developed Precocious Puberty. Final height was normal, but slightly lower than mid parental height in children with normal puberty. In spite of early diagnosis in this group of patients, precocious puberty was frequent, suggesting that other factors besides compliance are important. Other biomarkers of good metabolic control and treatments are needed to improve outcome.

P1-9

A Simulation-based Intervention Teaching Illness Management Skills to Caregivers of Children with Adrenal Insufficiency: a Randomised Controlled Study

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Background: Permanent adrenal insufficiency (AI) is an uncommon but potentially life-threatening condition in children. Patients are at particular risk during times of stress. Thus, caregivers should have good illness management skills. Despite frequent teaching and seemingly good knowledge of illness management we still see a reluctance of caregivers to administer intramuscular (IM) hydrocortisone at home when indicated, preferring instead to drive themselves to the emergency department or call emergency medical services, as previously described by other centers. Simulation (SIM) is increasingly used in medical education, but its use in teaching illness management to caregivers of children with AI has not been evaluated.

Objectives: To compare the impact of illness management teaching delivered using SIM or traditional teaching on caregiver's knowledge, ability and confidence with managing illness (including intramuscular hydrocortisone injection) in a child with AI.

Methods: Subjects were randomly assigned to SIM-based teaching or traditional teaching. All participants completed knowledge/self-confidence questionnaires and performance assessments using SIM scenarios, before and after teaching.

Results: 39 caregivers of mean age (SD) 40.2 (8.7) years, of children with AI of mean duration (SD) of 6.3 (4.7) years; were randomized to receive SIM-based teaching (N=20) or traditional teaching (N=19). 61.5% of participants were female.

	Within group comparisons *P<0.005	Traditional	SIM	
Knowledge Scores (Max score: 10)	Pre-teaching Post-teaching Change observed	7.0 (2.2) 8.3 (1.6) +1.1 (1.4)	7.8 (1.7) 8.4 (1.0) +0.5 (1.2)	p=0.226 p=0.838 p=0.186
Confidence Scores (Max score: 40)	Pre-teaching Post-teaching Change observed	29.3 (7.1)* 37.8 (3.0)* +8.6 (5.6)	31.5 (3.0)* 38.8 (1.6)* +7.4 (3.1)	p=0.225 p=0.232 p=0.416
SIM-scenario Scores (Max score: 26)	Pre-teaching Post-teaching Change observed	18.7 (5.4)* 23.4 (1.7)* +4.8 (5.8)	16.8 (5.6)* 21.7 (2.8)* +4.9 (6.3)	p=0.298 p=0.024 p=0.944

Conclusions: Caregiver confidence and performance, as assessed using simulated scenarios, improved significantly in both arms with no difference observed between SIM and the traditional teaching arms. Caregiver performance in both groups was sub-optimal at baseline. These findings highlight the importance of on-going teaching of caregivers of children with established AI and the need to refine our current teaching. The lack of difference between the 2 arms could be explained by the fact that both groups underwent the assessment using SIM-scenarios (pre- and post-) suggesting that incorporating these into the current standard of care teaching would be as beneficial as a SIM-based teaching session. Caregivers reported that they found the SIM-scenarios valuable and many encouraged their partners to subsequently participate in the study.

Global Practice of Glucocorticoid and Mineralocorticoid Treatment in Children and Adults with Congenital Adrenal Hyperplasia – Insights from the I-CAH Registry

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Introduction: Despite existing guidelines there is no unified approach to glucocorticoid and mineralocorticoid replacement in congenital adrenal hyperplasia (CAH). Consequently, treatment varies in adults and children as well as across countries.

Objective: We used data from the I-CAH Registry to identify geographical and temporal variations in the treatment with glucocorticoids and mineralocorticoids of children and adults with CAH.

Methods: Data extraction was conducted in January 2019. We analysed 4866 patient visits (31 centres from 16 countries) between 1982 and 2018 with regards to the type, dose and timing of glucocorticoid and mineralocorticoid replacement. Hydrocortisone dose equivalents were calculated as 20 mg hydrocortisone = 4 mg prednisolone = 750 mg dexamethasone = 25 mg cortisone acetate.

Results: Data from 618 patients (350 females, 268 males) were analysed. Information on the glucocorticoid treatment was recorded in 4831 visits for 598 patients. The most frequently used glucocorticoid was hydrocortisone in children (88%), prednisolone (51%) and dexamethasone (28%) in adults. Most children received three glucocorticoid doses per day (74%); adults frequently received one (49%) or two (34%) daily doses. Glucocorticoid doses varied across age groups, with the hydrocortisone-equivalent in mg/m²/day (median with interquartile range) of 13.4 (10.3–17.8) in 0-1 years, 12.0 (10.0–14.4) in 1-8 years, 12.9 (10.6–15.4) in 8-12 years, 11.8 (6.0–15.1) in 12-18 years, 5.6 (3.5–12.4) in 18-30 years and 9.4 (5.8–14.3) in over 30 year-old patients. 500 patients (80.9%) had mineralocorticoid replacement (4474 visits). Most patients (63.5% of children, 67% of adults) received fludrocortisone once daily. Relative mineralocorticoid doses were significantly different between age groups, with a fludrocortisone dose (mg/m²/day, median with interquartile range) of 312 (212–476) in 0-1 years, 140 (94–205) in 1-8 years, 54 (41–91) in 8-12 years, 51 (34–76) in 12-18 years, 41 (31–76) in 18-30 years and 85 (51–107) in over 30 years old patients. A significant reduction in the glucocorticoid doses for children of 0-1 years was noted after 2010: 15.0 (11.6–20.3) mg/m²/day to 12.2 (10.0–15.9) mg/m²/day ($p<0.001$); however, this was not found in other age groups. There was huge variation among different countries and centres regarding type, dose and timing of glucocorticoid and mineralocorticoid treatment.

Conclusion: Data available through the I-CAH Registry suggests international variations in hormone replacement therapy,

with a tendency for high doses in younger patients. Further evidence regarding the impact of different treatment regimens on health outcomes will help improve the medical management of patients with CAH.

P1-11

Assessment of the adrenal function in children with acute lymphoblastic leukemia before and after induction therapy with corticosteroids

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Background: Acute lymphoblastic leukemia (ALL) is the most common cancer in children. Corticosteroids are the cornerstone in treatment of pediatric ALL. Steroids can cause several side effects including secondary adrenal insufficiency with disruption of cortisol response to stress causing morbidity and even mortality in those children.

Objective: To assess the adrenal gland function of children with ALL before and after induction therapy with corticosteroids and identify who required replacement till gland recovery.

Methods: Newly diagnosed ALL cases during the period from December 2016 till end of January 2018 were recruited from pediatric hematology/oncology ward at Sultan Qaboos University Hospital. Basal Adrenocorticotrophic hormone (ACTH) and cortisol levels were done at 7:30 am before and after induction therapy with Corticosteroids. ACTH stimulation test using a standard dose of (250 mcg) was done for those with low cortisol after induction and hydrocortisone replacement was started in cases with abnormal test response with follow up every 4 weeks to check their serum cortisol till recovery of adrenal gland.

Results: Thirty-two patients with ALL were recruited; 62.5 % of them were males. The mean age of the cases was 5.94 years \pm 2.75. Nine patients (28.1%) was found to have low cortisol after induction phase who were given hydrocortisone replacement with follow up every 4 weeks till full recovery. There was a statistically significant difference in the mean basal cortisol level between pre-chemotherapy stage (mean \pm SD= 377.94 \pm 177.09) and post-chemotherapy stage (mean \pm SD= 167.03 \pm 131.31). The mean reduction in cortisol level was 210.91 (95% CI= 135.35 – 286.46) and p<0.01

Conclusion: Cortisol level assessment must be obtained after steroids discontinuation for all patients with ALL. Steroids replacement therapy should be started immediately if abnormal levels were detected and follow up is required.

P1-12

Trientine treatment mimicking severe hyperandrogenism

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Drugs can interfere with immunoassays causing false measurements. Trientine (triethylene tetramine dihydrochloride) is a chelator of copper and is used in the treatment of patients with Wilson's disease as alternative for penicillamine. Trientine mainly increases urinary copper excretion leading to a negative copper balance. Serum concentrations of trientine reached under treatment are not known. This is the first report of an interference of trientine with two chemiluminescence assays causing falsely high measurements of testosterone and androstendione.

A 16 year old German girl with recently diagnosed Wilson's disease treated with trientine (750 mg daily) presented with post-pill oligomenorrhea. She was mildly overweight (BMI 24.9 kg/m²), had no hirsutism or other signs of hyperandrogenism. In her serum extremely high levels of testosterone with 384 ng/dl (reference; < 45) and of androstendione with 720 ng/dl (reference; < 157) were repeatedly measured by chemiluminescence assays (Immulite, Siemens). Because of the apparent discrepancy with the clinical presentation the sample was re-measured by LC-MS/MS and found to be normal (testosterone 57 ng/dl and androstendione 116 ng/dl). In addition, 24h-urine collection contained normal amounts of androgen metabolites as determined by GC-MS.

A possible explanation of the false-high measurement of androgens in the two chemiluminescence assays was interference with the luminescence reaction of the assay including alkaline phosphatase and dioxetane phosphate. The chemiluminescence signal is inversely correlated to the read of our assays. In agreement with our hypothesis after spiking of human serum with pure substance of triethylene tetramine dihydrochloride (35 mg/ml serum) the measurement of two serum probes showed an increase of testosterone by 75 to 95 %. In addition, after discontinuation of trientine for two days our patient had normal serum values for testosterone (43 ng/dl) and androstendione (195 ng/dl) in the same chemiluminescence assays.

In conclusion, trientine can interfere with chemiluminescence assays causing false measurements. Therefore, immunoassay results have to be interpreted with caution in patients treated with trientine and should be confirmed by MS if values are unexpected.

P1-13

Cytokines and the impairment of puberty

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The changes of the immune reactivity, the production of hormones and the neuroendocrinical regulation of immune homeostasis are the entities closely connected with the puberty. There is evidence for the role of cytokines in securing of intersystemic interaction as well as for the influence of reproductive hormones on the cytokine production. However, the question as to the role of cytokine in the formation of delayed puberty continues to be relevant.

Objective and hypothesis: to study the characteristics of cytokine-hormonal interactions at teenaged boys with delayed puberty.

Method: Serum cytokine profile tumor necrosis factor-a (TNF-a), interleukin (IL) 1 β , 2, 4, 6, 10 and testosterone (T), estradiol (E₂), luteinizing hormone (LH), follicle stimulating hormone (FSH) levels of 82 delayed puberty adolescents were compared with 78 healthy controls.

Results: The serum IL1 β level was increased and TNF-a level was decreased in delayed puberty than healthy controls ($P>0.04$). The IL10 level was increased but no significant ($P>0.06$). There were showed no significant difference in IL2, IL4, IL6 delayed puberty and healthy controls. Correlation analysis showed that T had a negative relationship with IL1 β in delayed puberty and were not significant correlations in healthy controls. Level E2 had a positive relationship with TNF-a and IL6 in delayed puberty in contrast to a strong negative correlation E2 with IL2 and IL4 in healthy controls. Stepwise multiple linear regression analysis revealed combined influence of IL1B and TNF-a on the production of FSH ($p<0.01$) as well as TNF-a and IL10 on the correlation T/LH ($p<0.05$).

Conclusion: the existence of the relation between the exponents of hormonal panel and cytokine production may witness about the belonging of last to functioning of hypophyseal gonadal system at patients with delayed puberty. The impairment of neuroimmuno-hormonal regulation is one of the mechanisms of delayed puberty.

Key words: delayed puberty, neuroimmunohormonal regulation, cytokine.

Bone, Growth Plate and Mineral Metabolism

P1-14

Refractory hypercalcemia after Denosumab treatment in pediatric age: a case report

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Background: Denosumab is a new class of antiresorptive medication and a fully human monoclonal antibody of the IgG2 immunoglobulin isotype to RANKL. In fact, it binds with high affinity and specificity to RANKL, mimicking the inhibitory effects of Osteoprotegerin, resulting in rapid suppression of bone resorption. Denosumab is commonly used also in pediatric age for treatment of osteoporosis, malignancies, and other benign bone lesions, such as fibrous dysplasia, central giant cell granuloma and aneurysmal bone cyst (ABC). ABC is a rare benign skeletal tumor characterized by multilocular, expansile and osteolytic lesions. Treatment options are en bloc resection, intralesional curettage followed by bone grafting, sclerotherapy, radionuclide ablation, embolization, and radiotherapy. Since these approaches may be associated with severe and long-lasting morbidity especially in cases with spinal and large pelvic lesions denosumab has been advocated and used as alternative therapy. Nevertheless, studies focused on the pharmacokinetics and pharmacodynamics in children are limited and after treatment a phenomenon of bone turnover rebound associated or not with hypercalcemia has been described in adults and anecdotally reported in pediatric patients.

Objective: To describe serious adverse effects after high-dose denosumab therapy in ABC patients

Case Report: A 10 years old male with pelvic ABC diagnosis underwent high dose of denosumab (120 mg s.c for every month for 10 months).

4 months after stopping denosumab, the patient presented with a 2-week history of nausea and vomiting. Investigations identified raised serum calcium (3.87 mmol/L) with high Ca++ level (1.64 mmol/L) and creatinine, indicating acute kidney injury (1.7 mg/dL) and U.S. showed nephrocalcinosis. Serum phosphate and alkaline phosphatase were normal, 25-hydroxy vitamin D was low, and parathyroid hormone appropriately suppressed, with normal thyroid function. Total body CT scan and body X-ray excluded local or metastatic disease. Initially, hypercalcemia was treated with rehydration associated with intravenous furosemide (1 mg/Kg i.v.) with very poor response. For recurrent increase in serum calcium level 3 doses of Bisphosphonates i.v. (pamidronate 1 mg/Kg i.v.) in one week and then followed by 5 doses every 15 days (0.5 mg/kg i.v.) were administered, with improvement of clinical and biochemical parameters. Last calcium was 2.47 mmol/L and renal function was totally normalized (creatinine 0.6 mg/dL).

Conclusions: Our case report showed a severe symptomatic hypercalcemia in paediatric patient after discontinuation of treatment with denosumab in ACB.

The increasing use of denosumab needs urgent surveillance and increased awareness among clinicians and patients.

P1-15

The overweight and obesity decrease the growth potential in Mexican children and adolescents

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Background: The bone age (BA) assess the skeletal maturity and determine the children linear growth. Mexican children have a slightly delay in skeletal maturity before 10 years, but they reach in mean a BA 1 year in advance at the end of the puberty. On the other hand, Mexico has a high prevalence of childhood obesity and the adiposity has been associated with the BA advance in other populations. For the above, the overweight and obesity could be impact in the growth potential of Mexican children.

Aim: To compare the skeletal maturation of Mexican children and adolescents according to nutritional status; and to analyze the effect of the body mass index (BMI) changes on BA acceleration and the adult height prediction.

Methods: We conducted a cross-sectional study. We included 915 healthy children of Mexico City's Metropolitan area between 2017 and 2018 (range 5 to 19 years). The anthropometric measures of participants and their parents were obtained by trained staff. A hand PA radiography was taken and analyzed using BoneXpert software to determine automated BA and the adult height prediction (AHP). We constructed the BA curves with the average of the difference between BA and chronological age (CA) as function of CA by gender. We compare the curves of BA according to nutritional status (overweight and obesity vs eutrophics). In a second phase we follow-up 56 children for 1 year. We analyzed the impact of BMI changes on BA progression, growth velocity and adult height prediction.

Results: As shown in Figure 1, the boys with overweight or obesity have an acceleration in BA at 7.9 years of age and they are 1.8 years of BA ahead at the end of the puberty; in comparison, eutrophic boys have slightly BA delayed until 13.5 years ($p<0.01$). On the other hand, the girls with overweight or obesity had BA acceleration at 8 years, and they are 1.6 years of BA ahead at the end of the puberty; in comparison, eutrophic girls have slightly BA delayed until 11.5 years ($p<0.01$). In the follow-up, we identify that for each Z-score of increase in the BMI, the AHP decrease 0.9 cm (95% CI 0.2 to 1.7).

Conclusion: Mexican children and adolescents with overweight and obesity have BA acceleration at younger age in comparison with eutrophic children. The increase in the Z-score of BMI reduce the growth potential and the AHP.

P1-16

Normocalcemic Hyperparathyroidism in Children

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Normocalcemic primary hyperparathyroidism (NPHPT) has been recognized as a variant of primary hyperparathyroidism (PHPT) and it is characterized by elevated PTH with persistently normal concentrations of albumin-adjusted total and ionized calcium. It is related to increased risk in development of osteopenia/osteoporosis as well of parathyroid adenoma and hypercalcemia/hypercalciuria. In order to identify biochemical disorders of PTH in normocalcemic children we performed in all patients that visited our pediatric endocrine unit for two years a complete calcium metabolism: Ca, P, ALP, 25OHD, intact PTH. A total of 3060 patients - excluding those that consulted for vitamin D deficiency, Ca metabolism abnormalities or known renal pathology (i.e. Bartter syndrome) - were included. We identified 157 patients (5.1%) with hyperparathyroidism (PTH > 45 pg/ml, Horm Res Paediatr 2015;84:124-129) and normal total serum calcium levels; adequate data on laboratory results and follow up were available in 114 patients; 67 (58.7%) of them were vitamin D replete (25OHVitD > 30 ng/ml, group 1) and forty-seven were vitamin D deficient (41.3 %) (25OHVitD < 30 ng/ml, group 2). All patients were treated with cholecalciferol (8000-16000 IU daily). All patients in groups 1 and 2 who did not normalize their PTH (< 45 pg/ml) within 6 months of monotherapy with vitamin D, received additional calcium supplementation (1000 mg/day). Evaluation of calcium metabolism (Ca, P, ALP, 25OHD, 1,25OHD, PTH) was performed every 3 months. In 6 patients (4 from group 1 and 2 from group 2) elevated PTH did not respond to 6 months of combined cholecalciferol/calcium therapy. These patients were switched to the non-calcemic synthetic 1-25(OH)₂-vitamin D analogue, paricalcitol, at the dose of 2 mcg x 1-3/day. Evaluation of calcium metabolism (Ca, P, ALP, 25OHD, 1,25OHD, PTH, urine Ca/Cr) was performed every 3 months. Parathormone levels normalized in 5 patients by 3 months of treatment and in one by 10 months of treatment with calcium in serum and urine being within normal range for age during treatment in all patients. We propose that all normocalcemic children that are checked for vitamin D deficiency undergo concomitant measurement of PTH levels. Subclinical hyperparathyroidism (PTH > 45 pg/ml) should be treated with cholecalciferol (8000-16000 IU/day) and calcium supplementation (1000 mg/day) and if unresponsive after a minimum of 3 months, with paricalcitol 2-6 mcg/day in order to normalize PTH and protect their bone and general health. Further studies are needed to standardize this approach.

P1-17**Serum testosterone level at the age of 12 is an important determinant of the following gain of bone mineral apparent density in 18-year old males: a longitudinal study from puberty**

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Background: Many cross-sectional studies have demonstrated that serum testosterone concentration is an important biochemical predictor of bone mineral density in young males, but to our knowledge, no longitudinal studies have been carried out to support these cross-sectional data.

Aims: to examine the associations between serum testosterone concentration at the age of 12 and the following gain in bone mineral density until the age of 18 years.

Subjects and Methods: Eighty eight boys were investigated at the mean age of 12.1 (T1) and at 18.0 (T2) years of age. Total body (TB), lumbar spine (LS) bone mineral density (BMD) and bone mineral apparent density (BMAD) were measured by different DEXA scans at T1 and T2. Therefore TB and LS BMAD standard deviation scores (SDS) at T1 and T2, as well as their change (Δ), were calculated. Serum testosterone concentration, bone age and total physical activity (tot PA) by accelerometer were studied at both time-points.

Results: Serum testosterone concentration at T1 was positively correlated with TB BMD at T2 ($r=0.28$; $P<0.01$), Δ TB BMAD SDS ($r=0.47$; $P<0.0001$) and Δ LS BMAD SDS ($r=0.23$; $P<0.05$). When controlling for bone age and tot PA at T1, the correlation between testosterone at T1 and Δ TB BMAD SDS remained significant ($r=0.32$; $P<0.05$).

Conclusions: Serum testosterone concentration at the age of 12 is associated with the following relative gain in total body BMAD in 18-year old males suggesting that testosterone already at early puberty is associated with the following bone mineral accrual.

P1-18**Nephrocalcinosis in children with X-Linked Hypophosphatemia: prevalence and risks factors**

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X-linked hypophosphatemia (XLH) is diagnosed in children with clinical and or radiological signs of rickets, impaired growth

velocity, low serum phosphate levels associated with renal phosphate wasting, in the absence of vitamin D or calcium deficiency. Conventional treatment is made of phosphate and active vitamin D. However, nephrocalcinosis has been identified as a complication of this therapy. Its prevalence is about 25-40% in adult XLH treated patients. It was never characterized in large cohorts of XLH children. The purpose of our study was to evaluate the prevalence of nephrocalcinosis and identify risk factors associated to the occurrence of this complication.

Methods: We studied 117 children with XLH (74 girls and 43 boys) ranging in age from 6 months to 18 years (median 9.4). The diagnosis of nephrocalcinosis was established by systematic renal ultrasound. The evaluation was recorded at the 1st identification of nephrocalcinosis or, for patients without nephrocalcinosis, at the last available ultrasound. Kidney function was assessed through creatinine clearance. Potential risks factors included markers of clinical disease severity, i.e. short stature, lower limb deformities, dental abscesses, craniosynostosis, chiari malformation, bone fracture, bone surgery and deafness, markers of biochemical imbalance and treatment follow up i.e. observance, duration of treatment, mean dose of treatment during the last four years preceding the diagnosis of nephrocalcinosis or the last visit.

Results: 47 of the 117 patients (40.2%) developed nephrocalcinosis after 6.6 ± 3.8 years of conventional treatment. All patients had a normal renal function. Patients with nephrocalcinosis had been exposed to dose of phosphate supplements significantly higher at the time of nephrocalcinosis diagnosis than patients without nephrocalcinosis at their last visit, i.e. 44.2 ± 14.7 mg/kg/day versus 36.1 ± 9.7 mg/kg/day, $p=0.001$, respectively. Similarly, the mean dose of phosphate administered during 4 years prior to the study evaluation was significantly higher in patients with nephrocalcinosis than in patients without, i.e. 49.9 ± 20.5 mg/kg/day vs 42.2 ± 11.4 mg/kg/day, $p=0.012$, respectively. Patients with nephrocalcinosis displayed a better observance than patient without 84.8 % vs 64.7 % ($p=0.02$). Patients with nephrocalcinosis presented with markers of severe disease. In fact the prevalence of craniosynostosis 23.3 % vs 8.3 % ($p = 0.047$), chiari malformation 27.9 % vs 17.2 %, dental abscesses 50 % vs 34.8 % was higher in this group.

Conclusion: Nephrocalcinosis is a frequent complication of the conventional treatment. It is associated with higher doses of therapy which could be explained by the severity of the disease.

P1-19

Abstract withdrawn

P1-20

Long-term Teriparatide (rhPTH) treatment in children with syndromic hypoparathyroidism

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Background: Hypoparathyroidism is characterized by absence or inadequately low circulating concentrations of parathyroid hormone, resulting in hypocalcaemia, hyperphosphataemia and elevated fractional excretion of calcium in the urine. The use of activated vitamin D analogues and calcium supplements are recommended as the primary therapy. To avoid vitamin D and calcium side effects, subcutaneous recombinant human parathormone [rhPTH (1-34)] has been proposed for hypoparathyroidism treatment.

Objective: Our objective was to evaluate rhPTH (1-34) long term safety and efficacy in pediatric patients with genetically proven syndromic hypoparathyroidism.

Methods: The study was a 9.2-year self-controlled trial on six pediatric patients (four males, two females, age 9.4 ± 5.2 years) with syndromic hypoparathyroidism: three subjects with autoimmune polyendocrinopathy candidiasis ectodermal dysplasia (APECED) syndrome (one of those with intestinal malabsorption), two with DiGeorge syndrome and one with hypoparathyroidism-deafness-renal dysplasia syndrome. Hypocalcemic clinical signs and biochemical parameters (blood calcium, phosphorus, alkaline phosphatase and urinary calcium-to-creatinine ratio) were compared during conventional treatment and on rhPTH (1-34) (teriparatide, 12.5 µg twice a day).

Results: rhPTH treatment allowed a marked reduction, even not always complete withdraw, of calcium and calcitriol therapy. During rhPTH (1-34), mean blood calcium and alkaline phosphatase were not significantly modified, whereas significant reduction of the urine calcium-to-creatinine ratio (0.55 ± 0.32 vs. 0.16 ± 0.09 , $p=0.02$) and blood phosphorus (2.01 ± 0.23 vs. 1.69 ± 0.21 , $p=0.03$) was obtained. The number of tetanic episodes was reduced in four patients during teriparatide treatment. Renal ultrasound findings worsened in 3 patients (with nefrocalcinosis in 2 patients) and was unmodified in the other 3.

Conclusion: In the presented children with syndromic hypoparathyroidism, substitutive treatment with rhPTH (1-34) allowed to maintain adequate blood calcium and phosphorus levels, to normalize urinary calcium excretion, to reduce the tetanic episodes. In patients with low compliance or with intestinal malabsorption, its utilization should be considered, even to reduce vitamin D and calcium treatment side effects.

P1-21

Dual X-ray Absorptiometry in Children With Hypophosphatasia Treated with Asfotase Alfa: a Pooled Post Hoc Analysis

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Hypophosphatasia (HPP) is a rare, inherited, systemic disease characterized by deficient tissue-nonspecific alkaline phosphatase activity. Common manifestations in children include impaired skeletal mineralization, short stature, and reduced physical function. Asfotase alfa is an enzyme replacement therapy approved for treatment of patients of any age with pediatric-onset HPP. The utility of dual X-ray absorptiometry (DXA) as a diagnostic tool or measure of treatment effectiveness in children with HPP is unclear. This post hoc analysis pooled DXA data from 19 children with pediatric-onset HPP aged ≥ 5 to <18 years at enrollment who were treated with asfotase alfa for up to 7 years (median [min, max] age at enrollment: 10.4 [5.9, 16.7] y; treatment duration: 6.3 (0.1, 6.6) y; male: 79%) in 2 open-label, multicenter studies (study 006/008 [NCT00952484/NCT01203826]; study 009 [NCT01163149]). DXA was performed at Baseline and approximately every 6 months thereafter. Baseline height Z-scores generally reflected short stature in these patients (median [min, max]: -1.26 [-6.6 , 0]), necessitating height adjustment of DXA Z-scores. At Baseline, bone mineral density (BMD) Z-scores for whole body (including the head) and lumbar spine were <-2 in 17% and 28% of patients, respectively. Absolute values for whole body and lumbar spine bone mineral content (BMC) and BMD increased over time vs. Baseline, with significant increases at Last Assessment ($P<0.0001$). Whole body and lumbar spine BMC Z-scores also increased significantly from Baseline to Last Assessment ($P\leq 0.0056$); BMD Z-scores did not. Increases in whole body and lumbar spine BMC Z-scores correlated positively with Radiographic Global Impression of Change (RGI-C) scale scores (Pearson's correlation coefficients [r]=0.4–0.6 [$P\leq 0.01$]). No significant correlations were observed between BMD Z-scores and RGI-C. Significant correlations with Rickets Severity Scale scores were observed for whole body BMC Z-score and lumbar spine BMD Z-score (both $r=-0.4$ [$P\leq 0.02$]). Data from this post hoc analysis demonstrate that whole body and lumbar spine BMD Z-scores are not uniformly low (<-2) in children with HPP; therefore, these scores have limited utility in diagnosis of HPP or assessment of disease severity. Although absolute BMC and BMD values and BMC Z-scores increased over time, the relative contributions of asfotase alfa and natural accumulation of BMD due to growth were unclear, as BMD Z-scores did not change. Based on these data, DXA may not be a useful tool in assessing bone deficits in patients with HPP. Other complementary measures may need to be considered.

P1-22**Differences in bone strength and cortical bone parameters in young Swedish women with Type 1 diabetes**

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Background: The incidence of Type 1 diabetes (T1D) is rising globally and fractures are common.

Objective: To investigate bone health in young females with a T1D duration of at least 10 years in relation to healthy, matched controls.

Subjects: Twenty-three Swedish females, aged 19.2–27.9 years, with a T1D duration of ≥10 years, were recruited from the Swedish National Diabetes Registry (NDR). A healthy control group, matched for age, gender and geography was used for comparison.

Methods: Dual-energy X-ray absorptiometry and peripheral quantitative computed tomography (pQCT) were used to assess bone mass. Data regarding the T1D participants was retrieved from both the NDR and the national Swedish Paediatric Diabetes Quality Registry (SWEDIABKIDS). A questionnaire regarding current diseases, previous fractures and degree of physical activity was used.

Results: The individuals with T1D had an average diabetes duration of 18.9 years and a long-term suboptimal or poor metabolic control. No differences were found between the study groups for weight and body mass index (BMI). Females with T1D were significantly shorter than individuals in the control group.

No differences were found between the T1D and control groups for total, lumbar spine and femur areal bone mineral density, or for lumbar spine bone mineral content (BMC). Total body BMC was lower in the T1D group in comparison with the control group; however, this difference was no longer apparent when total body BMC was adjusted for BMI, physical activity and height.

Data from the pQCT measurements did not reveal any differences between the T1D and control groups for trabecular density, cortical area, cortical thickness, endosteal or periosteal circumference. However, a higher cortical density (when adjusted for BMI, physical activity and height) was observed for the T1D group, (p-value 0.020). The bone strength index of cortical bone, SSI, was significantly lower among females with T1D.

Conclusions: This study demonstrates decreased bone strength and altered cortical bone parameters in young females with long-duration T1D in comparison with healthy matched controls. These factors contribute to the health burden, which warrants further attention towards improving bone health in patients with T1D.

P1-23**Increased prevalence of overweight and obesity and its clinical predictors in children affected by x-linked hypophosphatemia**

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Background/Aim: X-linked hypophosphatemia (XLH) is a rare disease caused by inactivating mutations in the phosphate-regulating endopeptidase homolog X-linked (*PHEX*) gene, characterized by chronic hypophosphatemia. XLH children present with progressive skeletal deformities (leg bowing, waddling gait, poor growth and disproportional short stature), dental abscesses, and craniosynostosis. Most affected children have been treated so far with multiple daily phosphate supplements and oral active vitamin D analogs. This therapy corrects clinical, biochemical and a radiographic sign of rickets, nonetheless, does not restore stable level of serum phosphate. Scientific evidences support the role of serum phosphate level in fat mass acquisition, i.e. obesity, in the general population. Elevated Body Mass Index (BMI) are recurrently reported in series of adult XLH patients. In addition, XLH patients display chronic hypophosphatemia, despite treatment. Therefore we decided to address the clinical metabolic phenotype, beyond the abnormal skeletal phenotype, in children affected with XLH. The aim of our longitudinal observational study was to investigate the prevalence of obesity and associated factors in a large cohort of children with XLH.

Patients/Methods: We selected 172 XLH-children aged 5-20 years (113 girls / 59 boys). Anthropometric parameters (weight, height, BMI) were collected at birth and during follow-up at mean age of 5.3-8.2-11.3-15.9 years (group 1-2-3-4, respectively). In each group, subjects were classified based on International Obesity Taskforce (IOTF) cut off values of BMI for age and sex as overweight or obese (IOTF 25-30 or ≥30 kg/m², respectively).

Results: In each age-group, almost 1/3 of XLH-patients were classified as overweight/obese (29.4% vs 28.7% vs 27.5% vs 36.7% for group 1-2-3-4, respectively). Children without XLH-family

history had higher BMI-IOTF at every point of follow-up, compared to those with positive XLH-family history. Moreover, higher BMI-IOTF is significantly associated with treatment duration (23.3 ± 4.4 vs 23.8 ± 3.8 vs 25.2 ± 4.5 kg/m², for subjects with treatment duration of <5, 5-10 and >10 years, respectively, p for trend=0.025). Multiple regression analysis confirmed that treatment length ($\beta=0.17$, 95%CI=0.30-1.73, $p=0.005$) and absence of XLH-family history ($\beta=-0.13$, 95%CI= -0.12 - -2.21, $p=0.029$) are positively associated with higher BMI-IOTF.

Conclusion: 1/3 of XLH-children have phenotypically unfavourable metabolic profile expressed as increased and progressive overweight/obesity, despite phosphate supplementation. Absence of XLH-family history and length of treatment could be considered clinical factors associated with higher BMI-IOTF in XLH. BMI and metabolic profile should be carefully managed in children, and later adults, with XLH.

P1-24

Novel Homozygous LRP5 Mutations in Patients with Osteoporosis-Pseudoglioma Syndrome

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Background: Osteoporosis pseudoglioma syndrome (OPPG) characterized by congenital or early onset blindness with severe juvenile onset osteoporosis. OPPG is a rare autosomal recessive disorder due to loss of function mutation in the low-density lipoprotein receptor like protein 5 (LRP5).

Methods: Two patients (siblings) underwent clinical examination, including a complete ophthalmic evaluation. Diagnosis of OPPG was based on clinical examination and bone mineral density (BMD). The entire coding sequence of LRP5 was examined using target region capture followed by next generation sequencing.

Results: molecular analysis identified a novel homozygous c.351G>A, p.Trp117Ter variant on chr11:68115574 (hg19) EX2/CDS2 in both sibs. Their parents were heterozygous carriers.

Conclusions: One novel homozygous variant was demonstrated in two OPPG cases from Iran. This result expands the spectrum of disease-causing LRP5 mutations. Although this mutation has not been reported, its frequencies in normal population are very low.

Diabetes and Insulin

P1-25

Pathogenicity of GCK gene mutation c.364C>G (p.Leu122Val)

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Background: Over 800 different mutations in GCK gene have been reported in the Human Gene Mutation Database, the vast majority of which result in monogenic diabetes (Maturity Onset Diabetes of the Young, MODY type 2). The missense mutation p.Leu122Val is listed in that database as “disease-causing”. However, the National Center for Biotechnology Information ClinVar database (Variation ID 585919) reports that this mutation is of “uncertain significance”. Both databases refer to an Italian pediatric patient reported by Massa et al in 2001.

Objective: To report a pedigree of 3 patients affected with GCK mutation c.364C>G (p.Leu122Val) to support the pathogenicity of this mutation.

Cases: Proband (case 1) is an African-American female who was diagnosed with diabetes at 3 years of age. She was initially treated for type 1 diabetes with basal/bolus insulin. Her diabetes autoantibodies were negative and she required low doses of insulin. Her insulin was discontinued upon discovery of a mutation in the GCK gene suggestive of MODY type 2. Her HgbA1c has since ranged from 6.8 - 7.2% without insulin therapy.

Case 2 is the younger half-sister of case 1. She was initially seen at 3 years of age for an elevated fasting glucose level of 118 mg/dl (6.55 mmol/L) and HgbA1c of 6.4%.

Case 3 is the mother of case 1 and 2. She had a history of insulin-requiring gestational diabetes with her second pregnancy, and received metformin therapy for 8 months post-partum. At a clinic visit with her daughters, she was found to have a fasting glucose of 129 mg/dl (7.16 mmol/L) and HgbA1c of 6.3%.

Results: Genetic analysis in the three cases revealed GCK mutation c.364C>G (p.Leu122Val). The maternal grandmother of cases 1 and 2 also had genetic testing performed that was negative for the mutation.

The potential pathogenic role of this mutation was evaluated *in silico* by Polyphen2, SIFT, and Mutation Taster. The mutation was considered to be “probably damaging”, “damaging”, and “disease-causing” respectively by those bioinformatics tools.

Conclusions: To our knowledge, the GCK mutation c.364C>G (p.Leu122Val) has only been reported in a pediatric patient in Italy and was without a phenotypic description. The description of these three family members over two generations strengthens the supposition that this mutation is indeed disease-causing and of clinical significance.

Reference

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Myocardial function in asymptomatic children with type 1 diabetes

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Introduction: Diabetic cardiomyopathy is defined as myocardial dysfunction which is independent from any other ischemic, valvular or hypertensive etiology. It is a multifactorial condition caused mainly by a change in the myocardial structure leading sometimes to fibrosis especially in patients with poor diabetes control.

Aim: To assess whether type 1 diabetic children and adolescents have early echocardiographic signs of subclinical ventricular dysfunction and whether diabetes control has any influence, using conventional and nonconventional echocardiographic tools

Methods: prospective, analytical case-control design in which the patient group (G1) (duration of diabetes \geq 1 year) was matched for age and sex with a control group (G2). Each subject had conventional transthoracic echocardiography and tissue Doppler imaging with two-dimensional speckle tracking echocardiography. Early (E, E' wave) and late (A, A' wave) diastolic myocardial velocity (m/s) and the respective ratios; and systolic and diastolic function of the left ventricle (LV) and right ventricle (RV) were calculated and compared within both groups.

Results: G1 and G2 comprised 40 and 31 children aged 6.2 – 15.5 years. The control group (G2) included 31 healthy children similar in terms of age and sex. There were no significant differences between the groups concerning body-mass index, blood pressure or heart rate. Left and right ventricular systolic function and right ventricular diastolic function were comparable between G1 and G2. By contrast, LV diastolic function for G1 and G2 showed mean (SD) E (m/s): 0.76 (0.17) vs 0.72 (0.15) ($p = 0.24$), A (m/s): 0.63 (0.17) vs 0.59 (0.14) ($p = 0.031$), E/A: 1.74 (0.51) vs 1.88 (0.53) ($p = 0.023$), E' (m/s): 0.15 (0.02) vs 0.16 (0.02) ($p = 0.16$), A' (m/s): 0.68 (0.01) vs 0.63 (0.01) ($p = 0.048$), E'/A': 2.08 (-0.51) vs 2.31 (0.42) ($p = 0.045$). Longitudinal basal LV strain was -18.23 (-2.82) for G1 vs -20.94 (-3.93) for G2 ($p = 0.032$).

LV functional impairment was correlated with the duration of the diabetes; and HbA1C.

Conclusion: This study has shown early, asymptomatic diastolic left ventricular dysfunction which precedes systolic dysfunction. The data indicate that duration and control of diabetes are risk factors.

A Case of Neonatal Diabetes with Hyperferritinemia: A Distal PTF1A Enhancer Mutation

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Introduction: Neonatal diabetes, defined as the onset of diabetes within the first six months of life, is very rare disease. Several genetic factors caused to neonatal disease have been identified to date. *PTF1A* (*pancreatic transcription factor 1a*) play a key role in early pancreas development and cerebellar neurogenesis. Biallelic mutations in *PTF1A* have been reported in patients with pancreatic and cerebellar agenesis, whereas mutations located in a distal pancreatic-specific enhancer cause isolated pancreatic agenesis. In here, we present a case with neonatal diabetes, high ferritin level, and cholestasis and who has initially been misdiagnosed as hemochromatosis. Following further genetic analysis, distal *PTF1A* enhancer mutation have been identified.

Case: Two and half month male was referred to our hospital from another center because of hyperglycemia and cholestasis. He was born with a birth weight of 1830 gr at 36 gestational week from mother with oligohydramnios. The parents were relatives (first-degree-cousin). On physical examination, his weight was 1900 gr (<3p), height was 44 cm (<3p) and low ear, triangle face and micrognathia were observed. Both of testes were in scrotum (2/2 cc). In the laboratory, glucose 327 mg/dL, insulin 0.4 μ U/mL (2.6-24.9), c-peptide < 0.1 ng/mL (0.9-7.1), urine and blood ketones were negative, ammonia and lactate were normal, ferritin was 3057.58 ng/ml (50-200). Insulin infusion was initially started. Sequencing analyzes of *ABCC8/KCNJ11* were planned and glibenclamide was added. Because of persistent hyperferritinemia, abdominal MRI was performed and it was showed increased intensity in the liver, which is suggesting hemochromatosis. Therefore, *HFE* gene analysis was performed. In order to show tissue iron deposition, buccal biopsy was performed; however biopsy specimen was inadequate. Pump treatment was unsuccessful because of technical problems. NPH was added and normoglycemia was achieved. No mutation in *ABCC8/KCNJ11* was found; therefore, glibenclamide treatment was stopped. Because of inadequate weight gain and steatocrit in stool, pancreatic enzyme replacement was started. Analysis of *HFE* gene revealed no mutation and during the treatment, normal serum ferritin levels were achieved. Following further genetic analysis, a distal *PTF1A* enhancer homozygous mutation (g.23508336 G>T) was found. His mother and father were heterozygous for the same mutation.

Conclusion: Hyperferritinemia can be accompanied in cases with neonatal diabetes as an acute phase reactant. If no mutation is detected in *ABCC8* and *KCNJ11* in cases of neonatal diabetes, investigation of rare genetic causes should be kept in mind.

Key words: Neonatal diabetes, *PTF1A* mutation, hyperferritinemia

P1-28**Elevated anti-tissue transglutaminase antibodies in children newly diagnosed with type 1 diabetes do not always indicate celiac disease**

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Introduction: The prevalence of celiac disease is 5–10 times higher in patients with type 1 diabetes mellitus (DM) than in the general population. Therefore, celiac serology should be screened intermittently in type 1 DM patients. However, anti-tissue transglutaminase (anti-TTG) antibody elevation may be detected incidentally at the time of type 1 DM diagnosis and regress spontaneously during follow-up, without medical or dietary interventions.

Objective: The aim of this study was to determine the prevalence of spontaneous normalization of anti-TTG in type 1 DM patients with positive anti-TTG titers at time of DM diagnosis, and the factors associated with this phenomenon.

Methods: Patients who were diagnosed with type 1 DM between July 1999 and May 2018 and whose anti-TTG levels were tested at time of diagnosis were included in the study. Clinical, laboratory, and treatment data of the patients were recorded. Patients with high anti-TTG titer were divided into two groups for statistical analysis: those whose celiac serology was positive at diagnosis and spontaneously normalized during follow-up, and those who were diagnosed with celiac disease.

Results: A total of 294 patients (142 male[48.3%], 152 female [51.7%]) with a mean age of 9,08 years (1,08–17,75 years) were included in the study. Elevated anti-TTG titer was detected in 9.5% (n=28) of the patients at the time of diagnosis. Of these, 60.7% (n=17) were diagnosed with celiac disease with consistent biopsy findings, while 39.3% (n=11) exhibited spontaneous normalization of celiac serology. Patients who were later diagnosed with celiac disease had higher mean HbA1c level at time of DM diagnosis compared to the patients who showed spontaneous normalization of anti-TTG serology (11.2% vs. 8.9%; p<0.05). Anti-TTG titers greater than 10 times the upper limit at time of DM diagnosis were observed in 52.9% of the celiac patients, compared to 9.1% of the patients that showed spontaneous normalization (p<0.05) (Table 1). Anthropometric measurements and gastrointestinal symptoms did not differ significantly between the two groups (Table 1).

Conclusion: Type 1 DM patients may have high anti-TTG titers at the time of diagnosis. However, this is not always an indicator of celiac disease, and antibody titers may normalize during follow-up. In the literature, spontaneous normalization of anti-TTG antibody titers is reported in 35.4–59% of type 1 DM patients. Consistent with the literature, this rate was 39.3% in our study. For this reason, monitoring antibody titers should be considered for asymptomatic patients with mild anti-TTG antibody elevation at time of DM diagnosis before recommending gluten-free diet and referring for biopsy. Screening for celiac disease at least 6 months after type 1 DM diagnosis is a more rational approach.

P1-29**What hypoglycemia does to the heart: Impact of nocturnal hypoglycemia on cardiac repolarization in diabetic children**

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Background: Hypoglycemia is the most common and most feared complication of insulin treated diabetes. Though mostly asymptomatic, nocturnal hypoglycemia can be fatal in rare cases: sudden nocturnal death is more frequent in diabetic patients than in others. It is postulated that hypoglycemia related QTc prolongation contributes to cardiac arrhythmia and can lead to death in bed.

Objective: To evaluate influence of nocturnal hypoglycemia on QTc in children with type 1 diabetes.

Patients and Methods: In 25 (11f, 14m) children with type 1 diabetes (mean age 13.5 y, range 8.1-17.5) continuous glucose monitoring (iProTM, Medtronic Minimed) was performed for 5 days, and simultaneously, holter ECG (Schiller) was recorded during each night. All subjects had normal cardiac findings in clinical examination/echocardiography and normal values for potassium, calcium and magnesium. No patient was under medication known to affect cardiac function or repolarization. Nocturnal hypoglycemia was defined as every period with a sensor glucose measurement below 3.7mmol/l for at least 15minutes during documented nighttime. ECG was transferred to labchart and mean QTc was calculated by the Bazett formula for every episode of nocturnal hypoglycemia and compared to a period of the same duration preceding hypoglycemia.

Results: 41 episodes of nocturnal hypoglycemia were observed, 33 with ECG recording. Mean duration of hypoglycemia was 96min (range 15-365min). Nadir was below 3 mmol/l in 16 events and 3.0-3.7 mmol/l in 17 cases. No relevant cardiac arrhythmia was documented. However, mean QTc during hypoglycemia was significantly longer compared to normoglycemia (411+/-15 vs 405+/-18 ms, p = 0.005).

These changes were not dependent on age, HbA1c, diabetes duration, duration or nadir of hypoglycemia. The increase in QTc though was more pronounced in subjects with lower magnesium levels (p= 0.04).

Conclusion: This study evaluated changes in cardiac repolarization during nocturnal hypoglycemia. We could document a QTc lengthening and thereby potentially arrhythmogenic effect of nocturnal hypoglycemia in otherwise healthy children with diabetes. This is of special relevance in predisposed subjects or in the face of comedications. In such risk patients, nocturnal hypoglycemia has to be avoided even more aggressively. Based on these findings, it may be reasonable to perform a resting ECG in diabetic children. As higher magnesium values could have a protective effect, testing of these levels should also be considered.

P1-30

Effects of glycan4 protein on INS1E cell viability and insulin signalling

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Background: Glycan4 is a heparan sulphate proteoglycan. In addition to a membranebound glycan4, a soluble form exists. Human and rodent adipose tissue were identified as source of circulating glycan4. Glycan4 serum levels are associated with obesity and insulin resistance, as in type 2 diabetes (T2D). Because of its positive effect on insulin sensitivity, glycan4 might play a role in the development of obesity, insulin resistance, and T2D. We asked whether or not glycan4 plays a role in βcell function.

Methods: INS1E served as βcell model. Glycan4 mRNA and protein were detected by quantitative PCR and Western Blot, respectively. Rat adipose tissue served as control. INS1E cell viability was measured using WST1Assay. Cells were incubated with recombinant rat glycan4 over 6h, 24h, and 72h. To assess signalling, INS1E cells were incubated for 15 minutes with different stimulants (insulin, IGF1, glycan4, and glycan4 + insulin). Insulin signalling targets (phosphorylated and total InsR βsubunit, AKT, ERK) were detected by Western Blot and densitometrically analysed using ImageJ.

Results: Both glycan4 mRNA and protein were detected in INS1E cells in comparable amounts to rat adipose tissue. Moreover, we found that rat glycan4 mRNA expression is very high in the metabolic organs kidney, muscle, pancreas, and liver. WST1Assays revealed that exogenous glycan4 has no effect on INS1E cell viability in all tested conditions (low vs. high serum culture media, incubation times 672h, recombinant glycan4 protein of different manufacturers, and altered starting cell numbers). Consistent with these results, we detected no effect of glycan4 stimulation on INS1E insulin signalling. Whereas phosphorylation of insulin signalling pathway proteins InsR β-subunit, AKT and ERK increased with insulin and IGF1 as expected, treatment with recombinant glycan4 protein did not enhance phosphorylation of these proteins. Furthermore, combined treatment of INS1E cells with insulin and glycan4 did not lead to an increased phosphorylation of the insulin signalling pathway compared to sole insulin stimulation.

Discussion: Extensive testing of recombinant glycan4 stimulation did not result in any effect on INS1E cell viability or insulin signalling pathway. We will test the effects of downregulating or overexpressing endogenous glycan4 on INS1E cell function, and plan to measure glycan4 in serum samples of lean and obese children to unravel a possible association between glycan4 levels and parameters of obesity and insulin resistance.

P1-31

Abstract withdrawn

P1-32

Heterozygous RFX6 mutation as a cause of diabetes mellitus in a multigenerational family

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Background: Monogenic diabetes mellitus (DM) is an early-onset, non- autoimmune diabetes. Genetic diagnosis can personalize patient management and lead to prevention. We describe four generations of DM in one family, caused by a heterozygous mutation in the *RFX6* gene. *RFX6* (Regulatory factor X, 6) is essential for the development of the endocrine pancreas. Mutations in *RFX6* can cause neonatal (Mitchell-Riley syndrome) as well as childhood DM, intestinal atresia and hepatobiliary abnormalities.

Patients and Methods: Transient, stress hyperglycemia was the first clinical presentation of our patient at the age of 3 years. Non-autoimmune DM was diagnosed at 13 years. Maternal family history revealed great-grandmother, grandmother and a mother, two aunts and one cousin with DM. They were diagnosed as diabetics in adolescence or young adulthood. Only the patient's mother was treated by insulin.

Next generation panel sequencing for genes of monogenic DM, using the Trusight One platform (Illumina), was utilized for genetic analysis of the proband. Sanger sequencing was performed to validate the likely-pathogenic finding and for segregation analysis in the family.

Results: We identified a heterozygous mutation in *RFX6* gene (c.781-2_787delinsG affecting intron7/exon 8) in the proband that co-segregated in five family members with DM, and in the patient's healthy brother and two young cousins. One uncle who carries the mutation has asymptomatic DM. This mutation was previously reported to cause autosomal recessive neonatal diabetes.

Conclusions: Heterozygous *RFX6* mutation was diagnosed as the cause of familial DM. Genetic evaluation of youth with non - autoimmune DM provides accurate diagnosis and identifies subjects at risk.

P1-33**Plasma tocopherols and carotenes are decreased in Spanish children and adolescents with insulin resistance, independently of obesity**

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Introduction: Childhood obesity and insulin resistance (IR) are rising in prevalence, increasing the future adults' cardio-metabolic risk. One of the potential mechanisms behind these alterations is oxidative stress, fruit of increased free radical production and diminished antioxidant defense. Although low plasma vitamin concentrations and oxidative stress have been observed to be associated with obesity in adults and children, their association with IR in children is less clear.

Materials and Methods: 985 children (49.2% males, 71.7% prepubertal, 24.8% overweight, 47.1% obesity) were recruited for this study. Pubertal status was assessed and anthropometry (weight, height), systolic and diastolic blood pressure (SBP, DBP) and serum glucose, insulin, triacylglycerols (TAG) and high-density lipoprotein cholesterol (HDL-C) were measured. Plasma concentrations tocopherols and carotenes were determined with ultra-high-pressure liquid chromatography coupled to mass spectrometry and concentrations were referred to TAG. Glucose ≥ 100 mg/dL was considered hyperglycemia whereas HOMA-IR ≥ 2.5 in prepubertal males/females, HOMA-IR ≥ 3.38 in pubertal males or HOMA-IR ≥ 3.905 in pubertal females was indicative of IR. General linear models adjusted for sex, age, recruitment center and BMI were used to evaluate differences in vitamin concentrations, and multiple linear regression (including age, sex and BMI) was used

to evaluate the independent contribution of plasma tocopherols and carotenes to HOMA-IR values.

Results: Pubertal children with hyperglycemia showed lower tocopherols (0.094 ± 0.041 vs 0.130 ± 0.062 , $P=0.023$) and carotenes (8.21 ± 4.56 vs 14.83 ± 13.25 , $P=0.012$) plasma concentrations than those with normal glycaemia, independently of BMI. Prepubertal and pubertal children with IR showed lower tocopherol (Pre: 0.109 ± 0.044 vs 0.151 ± 0.066 , $P<0.001$; Pub: 0.102 ± 0.041 vs 0.136 ± 0.063 , $P=0.009$) plasma concentrations and prepubertal children with IR showed lower carotenes (10.03 ± 7.68 vs 22.35 ± 19.95 , $P=0.001$) plasma concentrations, both compared with children without IR. Linear regression analyses showed an independent negative association between plasma tocopherols and HOMA-IR values in prepubertal ($\beta_{est}=-0.138$, $P=0.001$) and pubertal ($\beta_{est}=-0.207$, $P=0.002$) children.

Discussion: Our findings agree with previous studies that showed decreased plasma concentrations of tocopherols and carotenes in children with obesity. However, we observe further implications of low circulating concentrations of tocopherols in terms of their negative association with hyperglycemia and insulin resistance in both prepubertal and pubertal children, independently of BMI. These results must be taken into account in the design of prevention and treatment strategies of obesity and its complications in glucose metabolism.

P1-34**Serum Dipeptidyl peptidase-4 Activity and its Relation to Insulin Resistance in Type 1 Diabetic Adolescents**

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Background: Insulin resistance (IR) plays a larger role in type 1 diabetes (T1D) disease process than is commonly recognized. Dipeptidyl peptidase-4 (DPP-4) is an enzyme that is expressed on almost all cell surfaces. It deactivates many bioactive peptides involved in glucose regulation; glucose-dependent insulinotropic polypeptide and Glucagon-like peptide-1.

Objectives: This study evaluates serum DPP-4 activity in adolescent patients with T1D compared to controls and investigates the relationship between DPP-4 activity and the development of IR in these patients.

Subjects and Methods: We examined serum DPP-4 activity in 50 T1D adolescent patients following up in the outpatient clinic of Diabetes Endocrine Metabolism Pediatric Unit, Children Hospital, Cairo University and 80 healthy controls. All subjects were assessed for IR using the equation for estimated glucose disposal rate (eGDR). Biochemical evaluation including glycated haemoglobin (HbA1c) and lipid profile were performed.

Results: The mean age and diabetes duration of T1D patients were 14.44 and 6.27 years, respectively. Our studied patients showed poor glycemic control with a mean value for HbA1c was 10.51%. IR was found in 80% of T1D patients (eGDR<9), and 34% of our patients were dyslipidemic.

A significant elevation of DPP-4 was found in the control group ($p=0.04$). T1D patients were classified into 3 groups according to serum DPP-4 tertiles (<2.3, 2.3-5.7, >5.7 ng/ml) there was a significant increase in BMI SDS ($p=0.01$) and total cholesterol ($p=0.041$) across the 3 groups. Significant correlation was only found between DPP-4 levels and insulin dose ($p=0.024$, $r=0.318$). DPP-4 level was found to be significantly higher in the group of patients with good glycemic control. No significant relation was found between DPP-4 activity and eGDR.

Conclusion: DPP-4 was found to be related to the state of adiposity rather than the diabetic process in adolescents with T1D. It seemed to be beneficial rather than being harmful and require inhibition. Our patients were resistant to insulin but this resistance mostly related to poor glycemic control rather than their serum DPP-4 activity.

P1-35

The impact of CGM availability: real world data from a population based clinic

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Real-world studies reporting the impact of continuous glucose monitoring (CGM) in children with Type 1 diabetes (T1D) are limited. In April 2017 CGM became fully subsidised in Australia for children with T1D <21 yrs. We report the impact of this in a large population based sample of paediatric diabetes (n=1093). Almost all (99%) children (age < 18 yr) with diabetes in Western Australia attend a single paediatric diabetes centre.

Prior to April 2017 6.5% of children were using CGM, 18 months following CGM funding the rate of usage was 76.1%. Mean age of the clinic group was 11.9 yrs with diabetes duration of 4.4 years; demographic and clinical characteristics of those on CGM were similar. Patients attend clinic every 3 mths. Prospective cohort analysis was used to determine change over time of key diabetes outcomes: HbA1c and severe hypoglycaemia (coma/convulsions).

The mean HbA1c (\pm SE) of all T1D (n=1093) for the 6 mths prior to CGM rollout was $8.2 \pm 0.05\%$. Mean HbA1c of the whole clinic reduced significantly at every 3 mth period up until 18 mths post rollout. At 18 mths, 75% of patients in the clinic were using

CGM and mean HbA1c was $7.76 \pm 0.06\%$ ($p < 0.001$ vs baseline). There was a 27 % reduction on severe hypoglycaemic events (3.1 to 2.25 SH/ 100 patient years).

Patients on insulin pump therapy had an HbA1c of 8.16% prior to commencing CGM therapy and at 3 mths post CGM start this has reduced to 7.92% ($p=0.002$). Patients on subcutaneous injection therapy had an HbA1c of 8.33% prior to starting CGM and HbA1c of 8.14% post ($p=0.226$).

These data suggest that in a population-based cohort of paediatric patients with T1D the introduction of CGM results in improved glycaemic control and reduced hypoglycaemia over 18 months. These real world data show similar outcomes to randomised controlled trials with CGM and add to the evidence for CGM use in clinical practice for all children with Type 1 diabetes.

P1-36

Expression of receptor for advanced glycation end-products and its ligands HMGB1 and s100A12 in children and adolescents with new-onset Type 1 diabetes and in patients with longer disease duration

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Background: Receptor for advanced glycation end-products (RAGE) is a multiligand receptor up-regulated at sites of inflammation, especially in tissues with accelerated advanced glycation end-products formation. It is additionally stimulated by RAGE ligands S100A12 and HMGB1 released from recruited immune cells thus perpetuating the inflammatory process with a potential role in the development of type 1 diabetes as well as in development in diabetes complications. Expression of RAGE molecules and its ligands has not been evaluated in new-onset diabetic patients, and data on their role in diabetes development are still scarce.

Aim: To assess gene expression for RAGE, S100A12 and HMGB1 in peripheral blood mononuclear cells (PBMC) and plasma concentration of truncated receptor sRAGE and CRP in patients suffering from new-onset type 1 diabetes (NT1D), in patients with disease duration of more than five years (T1D) and in healthy controls.

Subjects and Methods: We included 35 NT1D patients (47.5% female, age 10.7 ± 3.0 years), 36 T1D patients (47.2% female, age 16.3 ± 5.6 years), and 36 healthy controls (55.6% female, age 16.2 ± 6.9 years). Gene expression for RAGE, S100A12, and HMGB1 was quantified using qPCR, and sRAGE level was measured by ELISA. CRP was measured by routine laboratory method.

Results: The PBMC s100A12 gene expression (in arbitrary units, AU) was significantly lower in NT1D patients compared to controls (mean \pm SD (95%CI) = 1.22 ± 0.81 (0.94-1.51) v.s. 2.62 (2.01-3.23), $p=0.040$) and compared to T1D (3.07 ± 3.10 (2.02-4.12),

$p=0.002$). HMBG (AU) expression was also lower in NT1D when compared to controls (0.73 ± 0.63 (0.51-0.95) v.s. 1.91 (0.97-1.42), $p=0.031$) with no difference when compared to T1D. There was no difference between groups neither in RAGE gene expression nor in plasma sRAGE levels. NT1D also showed higher CRP (mg/dL) levels when compared to control group (2.32 ± 4.15 (0.77-3.87) v.s. 0.62 ± 0.95 (0.27-0.96), $p=0.023$).

Conclusion: Our findings might suggest the role of s100A12 and HMGB1 in type 1 diabetes development. However, we expected increased expression of these molecules in the setting of enhanced inflammation as suggested by higher CRP levels. We speculate that s100A12 and HMGB1 expression might be restricted to sites of inflammation harvesting PBMC expressing these genes from peripheral blood. Comparison between gene and protein expression in peripheral blood as well as between circulation and affected tissues should be performed in order to explain the contribution of these molecules to the development of diabetes.

P1-37

Association of maternal depressive symptoms with worse metabolic control in adolescents with Type 1 Diabetes

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Introduction: Metabolic control (MC) of patients with type 1 diabetes (DM1) is linked with complications in short and long term follow up. Adolescence is a critical period in the treatment of DM1, making it difficult to achieve good MC. Few studies, all conducted in the United States, have shown an association between mother's depressive symptoms with poorer MC of their adolescent.

Objective: To evaluate the association between maternal depressive symptoms and Metabolic control of adolescents with DM1 in chilean patients .

Patients and Methods: Cross-sectional observational study. Adolescents between 10 and 18 years of age, with a diagnosis of DM1 more than 1 year since the beginning of DM1, and their mothers were recruited . Beck II test (BDI-II), depression questionnaire Childhood (CDI), SALUFAM questionnaire and sociodemographic data questionnaire were applied. Hemoglobin was measured by capillary glycosylation (HbA1c), as a marker of metabolic control. For numerical variables, a T student test, and ANOVA were performed, and for categorical variables a Fisher's test. A significant $p <0.05$ value was considered.

Results: A total of 86 adolescents of 14.04 ± 2.3 years old and 5.95 ± 3.7 years of evolution and their mothers completed the study . 27.3% of mothers presented depressive symptoms, being associated with poorer metabolic control (HbA1c of 8.91% , vs 7.66% p value <0.001). The mother's depressive symptoms were associated with a lower maternal and paternal educational level, lower home income, number of children in the family, presence of

chronic diseases in siblings and health vulnerability. Between adolescents 17.6% had depressive symptoms, which were not associated with maternal depressive symptoms or worse metabolic control.

Conclusions: The presence of maternal depressive symptoms is associated with worse metabolic control in adolescents. A screening for depressive symptoms in mothers of adolescents with DM1 is recommended in order to achieve better metabolic results in adolescents with DM1

P1-38

The factors associated with high levels of HbA1C in children and young people with Type 1 Diabetes mellitus

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Introduction: Patients with diabetes are encouraged to achieve good glycaemic control to reduce the risks of complications. Many factors are associated with glycaemic control.

The objective of this study was to evaluate factors associated with good glycaemic control among a cohort of children and young people with type 1 diabetes in Lancashire United kingdom.

Methods: All children and young people with Type 1 diabetes being managed in the diabetic unit at Lancashire Teaching hospitals within the North West region of the United Kingdom were evaluated from April 2016 to March 2017. Patients were classified based on their HbA1C levels below 58 mmol/mol (Low HbA1C) and above or equal to 58 mmol/mol (High HbA1C). Sociodemographic and clinical factors were correlated with HbA1C levels.

Results: There were 195 total patients aged 4 to 19 years (mean age, 14.4 years) and 43.6% were females. The mean HbA1C of the cohort was 71 mmol/mol (SD 18), and 80% of the patients had high HbA1C.

Factors independently correlated with increased HbA1c levels included duration of diabetes, number of contacts with diabetic nurses and the use of continuous glucose monitoring system (CGMS) and free style libre. Significant factors associated with low HbA1C using univariate analyses included duration of diabetes with diagnosis duration less than 5 years ($p=0.002$) and use of continuous glucose monitoring system (CGMS) and free style libre ($p=0.001$).

Conclusions: Good glycaemic control was associated with diagnosis duration less than 5 years and use of continuous glucose monitoring system (CGMS) and free style libre. Therefore, management of patients focusing on these associated factors would be of great benefit in improving glycaemic control.

Fat, Metabolism and Obesity

P1-39

Differences between short- and long-term outcomes of laparoscopic sleeve gastrectomy in adolescence

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Background: Laparoscopic sleeve gastrectomy (LSG) has been established as a safe and effective bariatric procedure during adolescence, but its long-term results remain uncertain. Our aim was to report and compare the short- and long-term outcomes of LSG in adolescents.

Methods: We performed a retrospective analysis of patients submitted to LSG between 2010 and 2013 in our Institution. Baseline, short-term (1 year) and long-term (5-7 years) outcomes were evaluated. Outcomes included body mass index (BMI), percentage of excess weight loss (%EWL), surgical and clinical complications and co-morbidities resolution. Co-morbidities were classified as insulin resistance (HOMA-IR \geq 2.5), dyslipidemia (TC $>$ 200 or LDL-C $>$ 130 or HDL-C $<$ 40 for boys and HDL-C $<$ 45 for girls or TG $>$ 130 mg/dL), hypertension (systolic blood pressure $>$ 130 mmHg or diastolic blood pressure $>$ 80 mmHg) and hepatic steatosis (positive abdominal ultrasound). Surgical success was defined as %EWL $>$ 50%.

Results: A total of 11 patients were included (81.8% girls). Pre-operative mean age was 16.4 ± 1.4 years and mean BMI was 46.0 ± 5.0 kg/m 2 . At short-term follow-up, mean BMI and %EWL were 32.9 ± 3.6 kg/m 2 and 63.5%, respectively, with a success rate of 90.9%. Median long-term follow-up was 6.0 (4.8-6.9) years. At the long-term follow-up, mean BMI and %EWL were 42.9 ± 9.0 kg/m 2 and 28.3%, respectively, with a success rate of 27.2%. The mean %EWL were significantly different between the short and the long-term follow-up ($63.5\% \times 28.3\% ; p < 0.05$). No patient presented with diabetes at baseline. Hypertension, dyslipidemia, insulin resistance and hepatic steatosis were diagnosed in 63.6%, 90.9%, 90.9% and 36.4% patients at baseline. This prevalence decreased to 9%, 9%, 36.4% and 0% at short-term follow-up, but increased up to 45.4%, 54.5%, 72.7% and 18.1% at long-term follow-up. There were no intra or postoperative complications, but a total of 63.6% of patients underwent laparoscopic cholecystectomy and about half of the girls presented with anemia (hemoglobin $<$ 12 g/dL) within 5 years.

Conclusions: Adolescents who underwent LSG had a high success rate, and showed both weight and metabolic improvements, in the short-term. Nevertheless, although some adolescents were able to retain metabolic improvements, the long-term outcomes showed that they regained weight and reacquired cardiometabolic risk factors, implicating in a lower success rate. We also showed an increased risk of cholecystectomy and anemia among girls. Further studies should focus on identifying the subgroup of patients to whom LSG is highly successful in the long term.

P1-40

Late pregnancy exposure to mono(2-ethyl-5-hydroxyhexyl) phthalate affects weight z-scores in children up to 2 years

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Background: Endocrine-disruptor compounds (EDCs) like phthalates and bisphenol A (BPA) can have long term effect on children's physical growth. Studies have reported that effect of EDCs exposure on concurrent physical parameters like weight. But there is a knowledge gap with regards to long term effects of EDCs exposure on children's physical growth. Thus, in this study we evaluated the prenatal exposure of EDCs: BPA and phthalates and their influence on physical growth in children upto 2 years.

Methods: We selected 517 eligible participants from: Mothers and Children's Environmental Health (MOCEH) study in South Korea. MOCEH is a prospective multi-centric birth cohort study. We evaluated the effect of prenatal: first (early) and third (late) trimester of pregnancy, urinary BPA, mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-n-butyl phthalate (MBP) on z-scores of height, weight and body mass index (BMI) at 6,12 and 24 months using linear mixed model analysis.

Results: Linear mixed model analysis showed that late pregnancy MEHHP was associated with increase in weight z-score in children up to 24 months. Late pregnancy MEHHP significantly increased ($\beta=0.07, 0.01-0.13$) weight z-scores up to 24 months when all the EDCs together were included in one model for the mixed model analysis. We did not find significant results for early pregnancy EDCs exposure on z-scores of height, weight and BMI up to 24 months

Conclusion: Our results shows the long term effect of late pregnancy EDCs exposure: mono(2-ethyl-5-hydroxyhexyl) phthalate on weight z-scores up to 24 months. Our study identified the critical period of prenatal EDCs exposure affecting children's growth. Further, suggesting the need to explore the joint effects of exposure to mixtures of EDCs on children's health.

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P1-41**Growth arrest-specific 6 (Gas6) protein is associated with adiposity and metabolic syndrome in obese children and adolescents**

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Introduction: Growth arrest-specific 6 (Gas6) is a vitamin K-dependent protein produced by several types of cells including adipocytes and regulates their homeostasis. Previous studies indicate that Gas6 signaling may be involved in the pathogenesis of obesity and its complications, including systemic inflammation and insulin resistance. However, little is known about the clinical significance of the Gas6 system in childhood obesity. The aim of the study was to determine the potential association of circulating Gas6 with anthropometrical and metabolic status of obese children and adolescents.

Methods: In 74 obese children and adolescents (33 boys and 41 girls) in the mean age of 13.92 ± 3.14 years growth arrest-specific 6 (Gas6), glucose and insulin fasting and in oral glucose tolerance test (OGTT), HOMA-IR index and lipid profile were determined. Anthropometric parameters expressed as BMI Z-score, WHR, W/HtR and body composition was evaluated by bioelectrical impedance analysis (BIA) such as fat mass (FAT), fat-free mass (FFM), and total body water (TBW). Gas6 level was then correlated to the all anthropometrical and metabolic parameters. Patients were divided into two groups: with (26%) and without metabolic syndrome (MS), which were then compared for Gas6 level. The association for the Gas6 level and specific MS criteria was also assessed.

Results: Gas6 was significantly higher in MS patients (20.87 ng/ml vs. 13.64 ng/ml; $p < 0.05$). There was also significant positive relationship with number of MS criteria reached, and Gas6 level based on the ANOVA test ($p < 0.05$). Gas6 was also significantly higher in patients with abnormal triglycerides and HDL cholesterol levels ($p < 0.01$ and $p < 0.05$ respectively). Gas6 correlated significantly (positive) with BMI Z-score, FAT% ($p < 0.05$). There were also a negative significant correlation with FFM% and TBW% ($p < 0.05$). No significant associations were found with glucose and insulin metabolism parameters.

Conclusions: Circulating Gas6 levels are significantly associated with body composition (especially adiposity level) and is also related to the risk of metabolic syndrome development in obese pediatric population. The potential role of Gas6 signalling in the pathogenesis of childhood obesity and its complications requires further investigation.

P1-42**De-novo and depot-specific androgen production in human adipose tissue - a source of hyperandrogenism in obese females**

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Background: Obesity in females is often associated with metabolic complications and hyperandrogenism but the role of adipose tissue (AT) in androgen synthesis remains unclear.

Aims/Objectives: Employing human subcutaneous and visceral AT and cultured adipocytes, we studied whether AT could be a source of androgens promoting hyperandrogenism in lean and especially in obese females.

Methods: Subcutaneous and visceral AT was collected during elective surgeries from lean and obese patients and from females undergoing bariatric surgery. Hormone levels were measured in serum. Furthermore androgens were measured by Mass-Spec analysis in the supernatants of cultured human preadipocytes and adipocytes, and in extracts from subcutaneous and visceral AT. Gene and protein expression of steroidogenic enzymes were determined in AT and in cultured cells.

Results: Obese females had elevated androgen levels (e.g. testosterone, androstanedione, DHEAs, and T-SHBG-quotient) in serum compared to lean females. Serum androgen levels were reduced in patients with weight loss after bariatric surgery. We found substantial amounts of testosterone in subcutaneous and visceral AT from lean and obese females (9.11 – 12.3 ng/g tissue) being significantly higher in visceral tissue of obese females (+35%, $p=0.024$) and in the supernatant of preadipocytes and adipocytes (0.22–0.55 ng/10.000 cells). Furthermore, Mass-Spec revealed that progesterone, testosterone, DHT and androstanedione were measurable in AT of both depots and cell culture supernatant of preadipocytes and adipocytes in culture. Measured steroids were higher in samples from obese females, with the highest difference for testosterone in visceral tissue (+687%, $p=0.032$). Steroidogenic enzymes, including StAR, Cyp11A1, Cyp17A1, Cyp19, Hsd3b2, Hsd17b3/6, CYP19, AR, LH-receptor, AKR1C2 and 3 and 5alpha-reductase I and II were expressed in most of the human AT samples and cultured adipocytes from both depots. We found a significantly higher expression of CYP19 in visceral AT of obese females. Furthermore we found depot-specific differences for the expression of the following genes: StAR, Hsd3b2, Hsd17b6, Cyp19 and AR. Interestingly AKR1c2 and 3 were highly expressed in both depots in lean and obese females with a highly significant upregulation in obese individuals. Therefore the backdoor pathway for steroidogenesis might be a new mechanism and pathway for hyperandrogenism in obese females.

Conclusion: The whole steroidogenic machinery of the classical and backdoor pathway of steroidogenesis and capacity for androgen biosynthesis were found in both AT depots and cultured preadipocytes and adipocytes. Therefore, we hypothesize that AT is a de-novo site of androgen production and hence might add to the hyperandrogenism and irregular cycles in obese females.

P1-43

Association of biomarkers of endothelial dysfunction with MicroRNAs levels in overweight and obese adolescents

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Background and Aims: MicroRNAs play important regulatory roles in cholesterol homeostasis and endothelial dysfunction. The aim of present study was to characterize the expression of miRNAs in overweight/obese adolescents and to identify the possible correlation with metabolic profile and inflammatory biomarkers.

Methods: 79 overweight and obese adolescents aged 13.0 ± 2.0 years and 28 normal weight adolescents aged 13.7 ± 2.0 years were recruited. The concentrations of biomarkers of endothelial dysfunction (sE, sICAM-1, PAI-1, and fibrinogen) were measured by ELISA and the serum relative expression of miRNAs (miR-223, miR-33a, and miR-126) were determined by real-time quantitative PCR.

Results: The overweight and obese children presented increased levels of sE, sICAM-1, PAI-1, and fibrinogen compared with normal weight subjects. The overweight and obese adolescents also showed higher levels of miR-223 and miR-33a than normal weight subjects. No different level of miR-126 was observed between studied groups. By Spearman analysis, the levels of miR-223 positively correlated with age, weight, BMI, insulin, HOMA and PAI-1. The levels of miR-33a correlated with sICAM-1 in a positive manner and with HDL in a negative manner. The levels of miR-126 positively correlated with age and triglyceride.

Conclusion: The present study showed alterations of two miRNAs related to cholesterol homeostasis and endothelial activation in overweight and obese adolescents as compared with normal weight subjects. The correlation among miRNAs, metabolic profile,

and inflammatory biomarkers supported the use of some miRNAs extracted from serum samples as potential predictive tool for obesity.

P1-44

Metabolic Complications after Paediatric Liver Transplantation: A 10-year Longitudinal Study in a South-East Asian Population

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Background: Improved patient and graft survival post-liver transplantation has led to a parallel increase in metabolic syndrome (MS) reported in multiple centres. We aimed to study the prevalence and risk factors of metabolic complications in our paediatric liver transplant (LT) cohort.

Methods: This was a retrospective review of the LT database from 1995–2018. We studied the incidence of overweight, obesity (WHO BMI criteria), dyslipidaemia, hypertension and new onset diabetes after transplantation (NODAT) at 1 and 10 years post-LT. Age at LT, indication for LT, use of steroids, including pulsed steroid therapy for graft rejection and calcineurin inhibitors (CNIs) were recorded.

Results: There were 99 post-LT patients during this period, 43 were followed up to 10-years post-LT. Median (IQR) age at LT was 2.0 (1.3–4.7) years. The incidence of overweight and obesity at 1 and 10 years was 14.1% and 9.3% respectively. The most common metabolic complication was dyslipidaemia, affecting 20.0% and 9.3% of patients at 1 and 10 years post-LT; hypertension was found in 10.1% of patients 1 year post-LT and 4.7% of patients at 10-year follow up. The incidence of NODAT at 1 and 10 years post-LT were 2.0% and 4.7% respectively. The highest incidence of metabolic derangement was at 1 year post-LT; 34.3% patients had at least 1 metabolic complication, 10.1% had 2 or more, and 2.0% met criteria for metabolic syndrome. None of our patients fulfilled criteria for MS 10 years post-LT. The use of pulsed steroid therapy for acute graft rejection was significantly associated with dyslipidaemia ($p=0.006$) and hypertension ($p=0.05$) 1 year post-LT, as well as the development of NODAT ($p=0.001$). Median age at LT was significantly higher in those with NODAT (14 years) versus those without (2 years) ($p=0.001$).

Conclusion: Metabolic derangements are common in children in the first year post-LT, but appear to be less prevalent subsequently. Pulsed steroid therapy and older age at transplant (adolescents) are potential risk factors. The incidence of metabolic complications in our cohort is lower than that described in other centres. This could be in part related to the steroid weaning protocol and lower immunosuppression targets, which has seen lower metabolic complications without a corresponding increase in graft rejection rates. Nonetheless, post-LT patients are at risk of metabolic complications compared to the general paediatric population and would need longitudinal follow up for early detection and management of these complications.

P1-45**Non-Alcoholic Fatty Liver Disease and eGFR levels could be linked by the PNPLA3 I148M polymorphism in obese children**

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Background: The *patatin like phospholipase containing domain* 3 (PNPLA3) I148M polymorphism has an effect on modulation of estimated glomerular filtration rate (eGFR) in non-obese non-diabetic adults and in children with histologically confirmed Non-Alcoholic Fatty Liver Disease (NAFLD).

Objectives: To explored the impact of PNPLA3 I148M polymorphism on eGFR in obese children with and without NAFLD.

Methods: We genotyped 591 obese patients for PNPLA3 I148M polymorphism. Anthropometrical, biochemical and instrumental data were collected. NAFLD was defined by the presence of ultrasound detected liver steatosis and/or ALT levels >40IU/L.

Results: Patients with NAFLD showed significantly lower eGFR levels compared to subjects without NAFLD. Children with PNPLA3 MM genotype showed lower eGFR levels compared to those with either PNPLA3 IM or II genotypes both in presence and absence of NAFLD. A general linear model for eGFR variance, including gender, duration of obesity, PNPLA3 genotypes, HOMA, BMI-SDS, LDL-C and triglycerides as covariates, was performed both in patients with (model r^2 0.29; model $p=<0.0001$) and without NAFLD (model r^2 0.14; model $p=<0.0001$). It confirmed an inverse association between eGFR and PNPLA3 genotype only in the NAFLD group (p -value of PNPLA3 genotypes=0.03 in patients with and 0.94 in patients without NAFLD).

Conclusions: Children with obesity and PNPLA3 MM genotype show lower eGFR levels compared to other genotypes, with a major effect of this polymorphism in the presence of NAFLD.

P1-46**How to recognize underlying somatic causes of paediatric obesity? Performance of the diagnostic recommendations of the Endocrine Society Guideline and suggestions for improvement**

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Background: Underlying causes of obesity are thought to be rare even in specialized paediatric endocrinology clinics. However, evidence is limited. The Endocrine Society (ES) guideline for paediatric obesity makes the following diagnostic recommendations: endocrine evaluation in presence of reduced growth velocity, evaluation of cerebral obesity in presence of CNS injury, re-evaluation of drug choice in patients using antipsychotics. Genetic testing is recommended in presence of early-onset obesity <5 years combined with clinical features of genetic obesity disorders (e.g. hyperphagia) and/or family history of extreme obesity. Aim of this study was to evaluate performance of these diagnostic recommendations.

Methods: In this prospective observational study, children and adolescents with obesity visiting a specialized paediatric obesity centre were included. Extensive evaluation of endocrine, genetic, cerebral, medication-induced and lifestyle-induced causes of obesity was performed in all patients. Endocrine, cerebral, and medication-induced obesity were diagnosed only if onset of the underlying cause coincided with a clear slope discontinuity in the patient's growth charts. Genetic testing included next-generation sequencing panel of obesity-associated genes and microarray analysis. Lifestyle-induced obesity was diagnosed only in patients without a somatic diagnosis in whom the paediatric endocrinologist had clear arguments that lifestyle factors played the main role, e.g. changes in lifestyle factors coinciding with clear slope discontinuities in the growth charts. Performance of the guideline recommendations was evaluated using our extensive workup as external standard.

Results: We included 282 patients (59% female). Median age was 10.8 years (IQR 7.7–14.1); median BMI SDS +3.7 (IQR +3.3–+4.3). In 53 (19%) patients, underlying obesity causes were present: 36 genetic, 9 medication-induced, 8 cerebral. In 69/282 (25%) patients, lifestyle-induced obesity was diagnosed. The recommendations would have suggested diagnostics in only 36/53 patients with an underlying cause (sensitivity 68%; 95% CI 55%–79%). The ES guideline criteria ‘age of onset <5 years’ and ‘hyperphagia’ were discriminative for underlying diagnoses (p -value <0.001 vs lifestyle-induced obesity), whereas ‘family history of extreme obesity’ was not (p -value 0.09). Moreover, patients presenting with genetic obesity syndromes with typical onset of obesity >5 years (e.g., 16p11.2 deletion, Temple syndrome) and patients using weight-inducing medication other than antipsychotics would not have been identified if the guideline recommendations had been followed.

Conclusion: We here show that an extensive diagnostic work-up identified 32% more patients with underlying causes of obesity than the ES guideline would have. The guideline recommendations could improve by addition of other obesogenic drugs than antipsychotics, and more elaborate genetic testing instructions.

P1-47

How early is ‘extreme early-onset obesity’? Results of comprehensive growth curve analysis to identify genetic obesity disorders based on age of onset of obesity

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Background: Early-onset obesity is associated with genetic obesity disorders. According to the Endocrine Society guideline for paediatric obesity, genetic screening is indicated in selected cases with age of onset (AoO) of obesity <5 years. However, this cut-off value lacks evidence. Identifying genetic obesity is vital as treatment for leptin-melanocortin pathway disorders becomes available. We aimed to determine whether AoO of obesity is predictive for genetic causes in children with obesity and to identify the optimal cut-off value.

Methods: In this prospective observational study, patients visiting a specialized paediatric obesity center were included. All included patients underwent genetic testing (obesity gene panel and microarray analysis). Genetic obesity disorders were grouped

based on presence or absence of intellectual disability (ID). We compared AoO in genetic obesity patients to AoO in patients with lifestyle-induced severe obesity, which are patients without a somatic diagnosis (i.e., no genetic, endocrine, cerebral or medication-induced obesity) in whom lifestyle factors played the main role. AoO of obesity was determined by assessment of patients’ growth charts. Obesity was defined <2yrs as weight-for height >+3SDS for WHO median, and >2yrs as BMI-for-age >+2.3SDS. Performance of AoO (positive likelihood ratio; LR+, area under the curve; AUC) and optimal cut-off by Youden’s J were determined.

Results: In total, n=84 patients were included: 34 with genetic obesity (16 with ID and 18 without) and 50 with lifestyle-induced obesity. At screening, median age was 11.6 years (IQR 7.78–14.8); mean BMI +3.8SDS (SD 1.2). Mean number of growth measurements <5yrs was 11 (SD 5). Median AoO was 0.7 years (IQR 0.4–1.1) in genetic obesity without ID, 2.4 years (IQR 1.2–6.2) in genetic obesity with ID and 3.1 years (IQR 1.8–4.7) in lifestyle-induced obesity. AoO ≤1.0 years was the most optimal cut-off (sensitivity 53%, specificity 96%, LR+ 13.2) compared to the cut-off <5 years (sensitivity 82%, specificity 22%, LR+ 1.1). AoO performed well in identifying patients with genetic obesity without ID (AUC 0.903, p <0.001), but not for genetic obesity with ID (AUC 0.555, p =0.735).

Conclusion: Age of onset of obesity, with optimal cut-off value ≤1.0 years, is an appropriate predictor to identify which children with obesity without ID should undergo genetic screening and is more discriminative than the cut-off value <5 years stated in the guideline. However, for genetic obesity with ID, AoO of obesity was not discriminative compared to children with severe lifestyle-induced obesity referred to a specialized pediatric obesity center.

P1-48

Waist circumference triglyceride index is useful to predict non-alcoholic fatty liver disease in childhood obesity

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Objectives: We aimed to evaluate the performance of waist circumference triglyceride index(WTI) to predict non-alcoholic fatty liver disease(NAFLD) in obese children.

Methods: In this study 139 obese children(71 girls) were included(6-18 years). Height, weight, body mass index(BMI), waist circumference(WC), puberty stage, blood pressure, and biochemical values were obtained from the medical records. SDS and percentiles were calculated. The WTI was calculated as WC(cm)x triglyceride concentration(mmol/L). The total cholesterol/HDL-cholesterol index(TC/HDL-C) was calculated. NAFLD was showed by ultrasound. The AUC and appropriate cutoff points for WTI were calculated by ROC analysis.

Results: Anthropometric measurements, biochemical values and indexes in patients with and without liver fat are summarized in the Table 1. The WTI showed a positive correlation with weight($\rho=0.2$; $p=0.037$), insulin ($\rho=0.45$; $p<0.001$), HOMA-IR($\rho=0.44$; $p<0.001$), uric acid($\rho=0.97$; $p<0.001$), TC($\rho=0.35$; $p=0.004$), TC/HDL-C($\rho=0.46$; $p<0.001$) and triglyceride($\rho=0.957$; $p<0.001$). It was found that WTI values could be used to diagnose hepatosteatosis[AUC=0.65 (0.56-0.75); $p=0.002$]. Sensitivity and specificity values for $WTI \geq 190.4$ cases were found as 51% and 75%, respectively. The cut-off points for WTI were AUC=0.71; $p=0.003$ (sensitivity=53%, specificity=82%) in males and AUC=0.67; $p=0.003$ (sensitivity=57%, specificity=75%) in pubertal.

Conclusion: The WTI is a powerful and easy tool to predict NAFLD in childhood and is correlated with uric acid level. This is the first study assessing the accuracy of WTI in childhood obesity.

Table 1.

NAFLD Variable	No(n=71)		Yes(n=68)		p
	Mean±SD	Median(IQR)	Mean±SD	Median(IQR)	
Age,year	10.7±0.5	11.8±0.5	0.001		
Gender	Girl(71)	44(31.7%)	27(19.4%)	0.011	
	Boy(68)	27(19.4%)	41(29.5%)		
WeightSDS	2.49±0.19	3.05±0.17	0.009		
BMI	27.64(5.22)	30.7 (4.82)	<0.001		
BMI%SDS	2.51 (0.79)	2.7 (0.7)	0.007		
BMI%	99.4% (2.1)	99.7 (0.8)	0.004		
WC,cm	84.8±2.2	95.3±2.6	<0.001		
SystolicBP,mmHg(n=102)	114(11)	120(14)	0.015		
DiastolicBP,mmHg(n=102)	71±2	72±2	0.028		
Fasting glucose,mg/dl	89±2	90±1	0,561		
Insulin,uU/ml	12.7(10.6)	15.5(8.9)	<0.001		
HOMA-IR	2.51(2.43)	3.34(2)	<0.001		
ALT,IU/L	16(9)	25(17)	<0.001		
Uric acid,mg/dl(n=135)	4.7±0.9	5.5±1.3	0.046		
Cholesterol,mg/dl	175±6.4	178±4.7	0.33		
Triglyceride,mg/dl	96(62)	119(61)	0.046		
HDL-C,mg/dl(n=138)	45(15)	47(14)	0.272		
LDL-C,mg/dl(n=134)	105±5.7	106±4.1	0.239		
TC/HDL-C,(n=138)	3.98(1.23)	3.9(1.4)	0.002		
WTI	165(75)	198(109.7)	<0.001		

P1-49

Gut Microbiome of North-American Children with and without Prader-Willi Syndrome (PWS)

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Introduction: Prader-Willi Syndrome (PWS), a common syndromic form of childhood obesity, is characterized by failure-to-thrive during infancy followed by progressive hyperphagia and obesity in childhood. The pathogenesis of hyperphagia and weight-gain in PWS is poorly understood and management strategies have had variable and limited success. Several studies support an etiological contribution of dysbiotic gut microbiota in the metabolic derangements of obesity; however, the specific role of the gut microbiome in PWS is not fully understood. This study aims to characterize the gut bacterial and fungal composition of children with and without PWS.

Methods: A stool sample, 3-day dietary record, hyperphagia questionnaire, and anthropometric measures (height, weight, waist-circumference) were collected. Composition of the bacterial and fungal community in stool samples was assessed by 16S rRNA and ITS gene amplicon sequencing, respectively. Operational taxonomic units (OTUs, clustered at 97% identity using Mothur [v.1.39.5]), differences in α - and β -diversity indices (α : Shannon, Simpson, Chao1; β : Jaccard, Bray-Curtis) and differential abundance testing (DESeq2, R-package) were assessed between PWS and control groups. Relationship of PWS-status (with or without PWS) and weight status (normal-weight vs. overweight) to OTU-level profiles (bacterial&fungal) were investigated using canonical correspondence analysis.

Preliminary Results: Fifty children aged 3-17 were recruited [$n_{PWS}=25$ (14F:11M; median-age=6.3y; median BMI-z-score=0.83); $n_{control}=25$ (9F:16M; median-age=8.8y; median BMI-z-score=0.73)]. There was greater bacterial richness in the PWS-group compared to the controls (Chao1; $p=0.02$). No differences in other diversity indices were noted for the bacterial profile. β -diversity (Bray-Curtis) was significantly different for the fungal profile among PWS and control groups (Adonis function; $p<0.001$). Differential abundance testing identified five bacterial and one fungal OTU that were differentially abundant between PWS and control groups. Bacterial OTUs related to *Propionibacterium acnes* ($p=0.007$), *Staphylococcus* ($p<0.001$), unclassified members of *Enterobacteriaceae* ($p=0.001$), and *Lachnospiraceae* ($p=0.009$), and a fungal OTU classified as *Candida albicans* ($p=0.03$) were overrepresented in PWS compared to the controls. The PWS group was also characterized by lower relative abundance of an OTU related to *Akkermansia muciniphila* ($p<0.006$). The relative abundance of the genus *Prevotella* was significantly higher in the PWS group compared to normal weight children without PWS ($p=0.01$).

Conclusion: Differences were observed in α -& β -diversity indices between groups. Higher differential abundance of taxa associated with inflammation and obesity and lower differential abundance of taxa linked with improved metabolic outcomes were observed in PWS compared to controls. Characterization of microbiota functional differences between groups is currently ongoing.

P1-50

Two-year outcomes of Whānau Pakari: a novel home-based intervention for child and adolescent obesity

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Background: Whilst multi-disciplinary intervention models for children and adolescents with obesity remain recommended best practice, there is a lack of long-term outcome data, especially in home-based models and programs embedded within the clinical setting. Whānau Pakari is a community-based multi-disciplinary assessment/intervention programme for child obesity, focused on reducing health inequity. Based in Taranaki, Aotearoa/New Zealand, it focusses on high-risk groups (predominantly Māori and those from high deprivation).

Objectives: To determine whether 12-month BMI SDS reduction persisted at 24 months in this randomised controlled clinical trial. Second, to determine whether secondary outcome measures showed improvement (e.g. cardiovascular fitness, sweet drink intake and health-related quality of life [HRQOL]).

Methods: This trial was embedded within a clinical 'real-world' setting, with a mixed urban-rural population. Participants (recruited 2012-2014) were aged 5-16 years, with a BMI $\geq 98^{\text{th}}$ centile or $>91^{\text{st}}$ centile with weight-related co-morbidities. Participants were randomised either to a low-intensity control (6-monthly home-based assessments), or an intense intervention (6-monthly assessments and weekly sessions for 12 months). At home visits, participants underwent clinical assessments, with physical and psychological wellbeing evaluated. Primary outcome was change in BMI SDS from baseline.

Results: 203 children were randomised (47% Māori [NZ's Indigenous population], 43% NZ European), 53% female, 28% living in the most deprived quintile, mean age 10.7 years, mean BMI SDS 3.12 (range 1.52-5.34). 121 participants (60%) were assessed at 24 months (n=53 control, n=68 intervention). The BMI SDS reduction observed at 12 months from baseline was not retained at 24 months in the intention-to-treat analysis [control -0.03 (95% CI -0.14, 0.09) and intervention -0.02 (95% CI -0.12, 0.08)]. Achieving $\geq 70\%$ attendance in the high-intensity intervention resulted

in a persistent BMI SDS reduction of -0.22 after 24 months (95% CI -0.38, -0.06). Sweet drink intake was reduced, water intake increased, and HRQOL improved in both groups, with improvements in cardiovascular fitness and behavioural difficulties in the high-intensity group.

Conclusion: In this population with high representation from Māori and those from most deprived households, the reduction of BMI SDS at 12 months did not persist at 24 months, a year after program completion. However, there were multiple improvements in health measures. Attendance was key to outcome, with high-attendance leading to a clinically meaningful and persistent reduction in BMI SDS.

P1-51

Pathogenic mutations and variants in KSR2 in a cohort of obese children

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Background: Kinase suppressor of Ras 2 (KSR2) gene codes for a scaffold protein modulating intracellular pathways that involve MEK/BRAF cascade and AMPK signaling. KSR2 plays an important role in energy balance regulation, and KSR2 mutations were reported to be associated with obesity and insulin resistance in mice and humans. In transfected cells, several KSR2 mutations lead to impaired fatty acid oxidation, which improved under metformin treatment¹.

Aim of the Study: To report genotype and phenotype in obese children harboring KSR2 mutations in order to extend knowledge on clinical spectrum and therapeutic options in affected patients.

Patients and Methods: In n=88 children with suspected monogenic obesity, genetic panel analysis for known mutations in obesity-causing genes including the KSR2 gene (transcript ID ENST00000425217, NM0000173598.4) was performed. Three patients (Pat1-3) showing KSR2 mutations and seven patients showing KSR2 variants were identified. Genotype and phenotype were evaluated.

Results: In Pat1, who showed early-onset obesity (BMI > 97th percentile (P) at 1 yr of age, > 99.5th P from 7 yrs onward) compound heterozygosity for KSR2 missense mutations (p.Arg224Trp and

p.Asp294Glu) was observed. Corresponding probably pathogenic mutations p.Arg253Trp*, p.Asp323Glu* have been previously reported¹. Pat1 underwent bariatric surgery at age of 21 yrs, with postoperative impressive BMI improvement (preoperative BMI 50.8 kg/m², postoperative BMI 34.8 kg/m²). Metformin therapy was interrupted after adverse gastrointestinal effects.

Pat2 showed early-onset obesity (BMI > 97th P at 4 yrs of age, > 99.5th P from 6 yrs onward). In Pat2, one heterozygous KSR2 missense mutation (p.Ala344Thr) was found. The corresponding pathogenic mutation p.Ala373Thr* was previously reported in one obese patient¹. Pat2 started metformin treatment at age 17 yrs. Follow up is pending. In Pat3, aged 3 yrs, extreme weight increase despite diet restriction was observed. In this patient, one novel heterozygous KSR2 mutation (p.His536Tyr) was detected.

Six patients showed the KSR2 variant p.Arg525Gln. One homozygous synonymous KSR2 variant p.Thr143Thr and one benign heterozygous KSR2 variant p.Arg434Gln were observed in one additional patient.

Discussion: This is the first case study on KSR2 obesity patients since the initial report by Pearce et al. 201³¹. KSR2 mutations seem to be more frequent in obese children than previously suggested. Metformin treatment and bariatric surgery may be considered as therapeutic options in affected patients. For deeper understanding of pathogenic mechanisms in KSR2 related human obesity and evaluation of therapeutic approaches, further studies are needed.

Literature: Pearce et al., Cell. 2013;155(4):765-77, *transcript ID ENST00000339824

P1-52

Effect of feeding mode on longitudinal body composition in early life

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Background: Excessive gain in fat mass (FM) during the first months of life, known as the critical window for adiposity programming, is associated with an increased risk for adiposity and cardiovascular diseases in later life. Early life nutrition (breastfeeding or formula feeding) might influence body composition (FM and fat free mass (FFM)) development in early life.

Aims: To investigate differences in sex-specific longitudinal weight-for-length SDS and body composition between exclusively breastfed (BF) and formula fed (FF) infants from birth to 24 months.

Methods: 219 exclusively BF (BF for at least 3 months) infants (120 boys) and 112 exclusively FF (start FF before 1 month) infants (65 boys) were followed in the Sophia Pluto Cohort in Rotterdam, The Netherlands. Anthropometrics were measured at 1, 3, 6, 9, 12, 18 and 24 months and weight-for-length SDS was calculated

by Growth Analyser (<https://growthanalyser.org/>). Body composition was measured at 1, 3 and 6 months by PEA POD (COSMED, Italy) and thereafter by DXA (Lunar Prodigy, GE Healthcare, UK) with vacuum cushion (465 75100, Schmidt, Germany). All DXA scans were analyzed using enCORE software version 14.10. Longitudinal growth and body composition development during the first 2 years of life were analyzed using linear mixed model analyses.

Results: Longitudinal weight-for-length SDS and FM% during the first two years of life were not different between BF and FF infants (p=0.55 and p=0.36, resp.). Girls had a higher FM% compared to boys at all time points and boys a higher FFM (both p<0.001). FFM was significantly higher in BF infants (p=0.038).

During the first 6 months of age, BF infants had a higher gain in FM% compared to FF infants (p=0.014), but this was followed by a significantly faster decline in FM% from 6-24 months compared to FF infants (p=0.002).

Conclusion: During the first two years of life, BF and FF infants have similar trajectories of weight-for-length and FM%. BF infants show a greater gain in FM% during the first months of life, but also a faster decline in FM% from 6 to 24 months compared to FF infants. BF infants also have a higher FFM. Girls have significantly more FM and boys more FFM regardless of feeding mode.

P1-53

Age of obesity onset could be the first indicator of future metabolic complications – preliminary data of prospective multicenter study

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Context: The unified approach for obese children can result in therapeutic failure as obesity is a symptom of several conditions. It was previously suggested that only children with obesity onset beyond age 6 years will develop the metabolic syndrome and T2D.

In turn, early childhood obesity carries a few times less risk of adult obesity comparing to that with the onset during juvenility.

Aim: We determine the clinical and biochemical profile of early-(E-Ob, up to 3 yrs) and late-onset (L-Ob; after 3 yrs) obesity.

Methods: We analysed detailed clinical and laboratory profiles of 240 non-syndromic obese children (116 girls; BMI >97%) aged 6.0-17.0 from 3 countries in the prospective 'multi-OMICS' study granted by ESPE Research Unit. E-Ob and L-Ob was found in 55 and 185 subjects, respectively.

Results: E-Ob and L-Ob children had comparable mean age (11.8 ± 2.2 vs. 12.4 ± 2.3 yrs resp.), sex distribution, BMI (30.7 ± 5.7 vs. 31.0 ± 4.7), z-score BMI (2.8 ± 0.5 vs. 2.8 ± 0.4), waist-to-hip ratio (0.88 ± 0.1 vs. 0.88 ± 0.1), waist-to-height ratio (0.59 ± 0.1 vs. 0.58 ± 0.01), systolic and diastolic blood pressure, acanthosis nigricans frequency as well as body composition parameters ($p > 0.05$). Family economic status, gestational age, birth weight, type of delivery, mother's obesity before or during pregnancy, weaning time, antibiotic therapy in the 1st year of life and parents' BMI have not influenced the age of obesity onset.

Glucose, insulin (both in OGTT), insulin/glucose ratio, HOMA-IR, total cholesterol, HDL-chol, triglycerides, TSH, fT4, cortisol, ferritin, uric acid, creatinine as well the frequency of liver steatosis (by ultrasonography) were not different between E-Ob and L-Ob groups. L-Ob was characterized by higher values of HbA1c ($p=0.007$) as well as higher ALT ($p=0.009$), AST ($p=0.019$) and GGTP activity ($p=0.007$).

Conclusions: Higher activity of liver enzymes and higher value of hyperglycemia marker in children with late-onset obesity could reflect the influence of previously suggested enhanced adrenal steroidogenesis and indicate their tendency to develop the metabolic syndrome and T2D.

blood levels of FGF21 have been associated with parameters of lipid/carbohydrate metabolism, and FGF21 is known to be increased in obesity. The prevalence of childhood obesity presents a constant yearly increase. However, there are limited data regarding the potential role of FGF21 in metabolic and cardiovascular disorders in the paediatric population. Our aim was to investigate FGF21 serum levels in metabolic disorders and in relation to endothelial function in children.

Methods: Seventy-eight children (8-16 years old) were classified as obese/overweight ($n=41$; 53% of total) and normal weight ($n=37$) defined by body mass index (BMI) percentiles for age and sex. Blood pressure, fasting blood glucose, lipid profile and FGF21 serum levels were assessed. Children with MetS were identified according to the International Diabetes Federation criteria. Endothelial function was assessed by the brachial artery flow-mediated dilation (FMD) technique and normalized to the shear stimulus [i.e. peak%FMD normalized to shear rate (normalized FMD)]. Non-parametric statistics were used to investigate the relationship between FGF21 and FMD (Spearman's rank correlation) and the differences between groups (Mann-Whitney test).

Results: In our entire population, there was a significant negative correlation between FGF21 and normalized FMD (Spearman's rho = -0.239, $p=0.035$).

In obese/overweight children, FGF21 serum levels were significantly increased [median 73.6 (interquartile range 41.6-127.8) vs. 30.4 (13.9-92.6) pg/ml, $p=0.017$] and normalized FMD was significantly lower [0.06 (0.04-0.09) vs. 0.09 (0.04-0.12), $p=0.044$] compared to normal BMI children.

Children with MetS ($n=8$; 10% of the population) had significantly higher FGF21 serum levels compared to normal BMI ones [127.8 (75.9-261) vs. 30.4 (13.9-92.6) pg/ml, $p=0.005$]. Normalized FMD was lower in MetS children compared to those with normal BMI without, however, reaching statistical significance [0.07 (0.04-0.08) vs. 0.09 (0.04-0.12), $p=0.14$].

Conclusions: FGF21 serum levels were negatively correlated to normalized FMD in our paediatric population. FGF21 serum levels were increased in both obese/overweight and MetS children compared to those with normal BMI. Obese/overweight children also showed impaired endothelial response to FMD. Therefore, FGF21 shows promise as a novel biomarker for identifying early in life metabolic disorders and a potential risk for development of cardiovascular disease.

P1-54

Augmented Fibroblast Growth Factor 21 Serum Levels in Metabolic Disorders and Association With Endothelial Function in Childhood

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Introduction: Obesity and the metabolic syndrome (MetS) are linked to increased risk for endothelial dysfunction which is considered as the first step in the progression of cardiovascular disease. Fibroblast growth factor 21 (FGF21) is a protein with known effects on various metabolic pathways. In adults, the circulating

P1-55**A novel recurrent heterozygous *PLIN1* mutation in three Russian patients with partial lipodystrophy, dyslipidemia and insulin resistance**

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Introduction: The *PLIN1* gene encodes perilipin - a lipid droplet coat protein expressed in adipocytes where it inhibits basal and facilitates stimulated lipolysis. Mutations in *PLIN1* have been described in several families with partial lipodystrophy, dyslipidemia and insulin resistance (partial lipodystrophy type 4, Familial, FPLD4). Herein we describe a novel heterozygous c.1210-1delG splicing variant in *PLIN1* gene in three unrelated Russian patients with FPLD4 phenotype.

Subjects and Methods: Two girls (14 and 15 years) were referred to our clinic with suspicion of acromegaly, one girl (14 years) was referred with polydipsia, polyuria. All three patients shared similar clinical and metabolic findings: acromegalic features, loss of subcutaneous fat from extremities, excess fat depots of the face and neck, prominent muscular appearance of the calves, acanthosis nigricans, hirsutism, steatohepatitis, mild hypertension; hypertriglyceridemia and insulin resistance. 2 of 3 girls had mild diabetes mellitus. One girl had a history of recurrent pancreatitis and partial resection of the pancreas due to pancreatic necrosis. Her mother had the similar phenotype. The family histories of the two other patients were unremarkable.

Molecular genetic analysis using a custom Ion AmpliSeq next generation sequencing 'Lipodystrophy' panel and PGM sequencer (Thermo Fisher Scientific, USA) was performed in all three subjects. NGS results were confirmed by Sanger sequencing. Total RNA was isolated from subcutaneous fat obtained by a needle biopsy in one of the patients. cDNA was synthesized using random hexamer primers and *PLIN1* transcripts covering exons 8-9 were amplified by PCR and sequenced.

Results: A novel heterozygous c.1210-1delG mutation in intron of *PLIN1* gene was found in all three subjects. Sequencing of cDNA showed an abnormal 3' end *PLIN1* transcript.

Conclusion: The novel splicing variant is predicted to result in synthesis of an aberrant C-terminal part of PLIN1 protein suggesting, similar to the previously reported cases of FPLD4, an existence of the uniform molecular mechanism in the development of this disorder.

P1-56**Carotid intima-media thickness relates rather to epicardial and perirenal fat than total body adiposity in apparently healthy children**

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Background: Carotid intima-media thickness (cIMT) is a well-known marker of subclinical atherosclerosis. The distribution of adipose tissue among visceral fat reservoirs rather than the total adipose tissue mass is more likely to be related to subclinical atherosclerosis.

Objective: The aim of this study was to determine whether epicardial and perirenal fat are more related to cIMT than body adiposity in prepubertal children.

Methods: cIMT, epicardial and perirenal fat thickness were assessed by ultrasonography in 239 school-age Caucasian children [139 boys and 100 girls; mean age 8.9 ± 0.1 yr] included in a cross-sectional study of cardiovascular risk factors in prepubertal children.

Results: Epicardial and perirenal fat, but not waist or fat mass, were independent predictors of cIMT in all children ($\beta = 0.223$, $p = 0.001$; $\beta = 0.290$, $p < 0.0001$, respectively. Total $R^2 = 19.1\%$) as well as in lean ($\beta = 0.187$, $p = 0.029$; $\beta = 0.347$, $p < 0.0001$, respectively. Total $R^2 = 20.6\%$) and in obese children ($\beta = 0.279$, $p = 0.009$; $\beta = 0.240$, $p = 0.023$, respectively. Total $R^2 = 16.2\%$).

Conclusions: cIMT relates to epicardial and perirenal fat thickness, rather than to body adiposity, in healthy prepubertal children. Measurement of visceral fat thickness by ultrasonography may serve as a simple tool for cardiometabolic risk assessment in childhood.

P1-57**Put your money where your mouth is: preliminary evidence that oral microbiota diversity may shape later cardiometabolic health in children**

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Background: Emerging evidence suggests a link between the intestinal microbiota and cardiometabolic outcomes in both children and adults. The oral microbiota is less studied, and the association between the oral microbiota and cardiometabolic health in childhood remains largely unknown.

Objective: To explore the associations between oral microbiota diversity measured at 8-10 yr and cardiometabolic health in childhood and adolescence.

Methods: Data stem from the QUALITY cohort, a prospective cohort study of 630 children aged 8-10 years at recruitment, with a parental history of obesity. 16S-rRNA based microbial profiling of oral plaque samples obtained at baseline from 80 participants (40 normal weight, 40 overweight/obese) were performed to determine diversity of the oral microbiota. Measures of diversity include Observed OTUs, Chao1, Shannon and Simpson reciprocal indices. Measures of cardiometabolic health were assessed at 8-10 yrs, 10-12 yrs and 15-17 yrs, and include: fasting blood glucose, glucose 2hr post oral glucose load, homeostasis model of assessment (HOMA-IR), lipid profile (LDL cholesterol, HDL cholesterol and triglycerides), as well as age-, sex-, height-adjusted systolic (zSBP) and diastolic (zDBP) blood pressure z-scores. Pearson's correlations were used to estimate associations between diversity indices and cardiometabolic outcomes.

Results: LDL cholesterol at 8-10 yr was positively correlated with all indices of microbiota diversity (Obs OTUs r=0.23, p=0.046; Chao1 r=0.22, p=0.055; Shannon r=0.24, p=0.035; Simpson reciprocal r=0.22, p=0.049). While correlations remained positive for LDL measured at 10-12 yr and 15-17 yr, they did not reach statistical significance. Similarly, microbiota diversity was positively correlated with zSBP at 8-10 yrs (r=0.22-0.25) and 10-12 yrs (r=0.22-0.25), not reaching statistical significance at 15-17 yrs. Indices of diversity at 8-10 yr were negatively correlated with fasting glucose (r=-0.27 to -0.31) and glucose 2hr post load (r=-0.27 to -0.29) 7 years later (at 15-17 yrs). Microbiota diversity was not correlated with HOMA-IR.

Conclusions: These preliminary data in a small sample of children followed over 7 years suggest that oral microbiota diversity in early childhood may influence cardiometabolic health in later adolescence.

P1-58**A case-control study of exposure to bisphenol-A and phthalates in obese children**

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Background: The increasing incidence of obesity is a serious global public health challenge. Endocrine disrupting chemicals (EDCs) are exogenous chemicals that interfere with the endocrine system, including adipose tissue. Increasing evidence from epidemiological, animal, and *in vitro* studies shows that EDCs, in particular bisphenol A (BPA) and phthalates (e.g. di-ethyl-hexyl-phthalate, DEHP), can affect body weight, adipogenesis and circulating lipid profile, with potential transgenerational effects.

Objective: The aim of this study was to investigate the exposure to BPA and DEHP in a cohort of children with idiopathic obesity (IO).

Methods: A case-control study was conducted in 122 children. The study population comprised: 36 girls with IO (mean age 8.37 ± 1.64 years), 30 boys with IO (mean age 8.6 ± 1.57 years), 27 girls controls (mean age 6.67 ± 2.3 years) and 29 boys controls (mean age 6.46 ± 2.93 years). Urine BPA and DEHP metabolites were measured by gas chromatography and high-performance liquid chromatography, coupled with mass spectrometer (LC-MS/MS). Metabolic and hormone levels were assessed. Individual environmental exposure was evaluated through "ad hoc" questionnaires providing data on life styles, diet and other potential determinants of exposure.

Results: Both BPA and DEHP metabolites were measurable in all tested samples, including those from control group. Obese girls showed significantly higher BPA urinary levels than controls: median BPA $11.82 \mu\text{g/g}$ creatinine (range 3.8-23.15) vs $5.36 \mu\text{g/g}$ creatinine (range 3.02-10.85), respectively ($p<0.001$). No significant difference in DEHP metabolites level was found.

In obese girls, a positive correlation between BPA levels and adiponectin was found ($r=0.4$, $p<0.05$). Furthermore, phthalate levels positively correlated with leptin ($r=0.35$, $p<0.05$).

In obese boys no significant difference in EDC levels was revealed. Also, no significant correlation between EDC levels and other metabolic/endocrine parameters was observed.

A higher risk of being obese has been found in children with BPA levels above the median values with the habit to eat food packaged in plastic ($OR=11.09$, 95% CI=1.28-95.78).

Conclusions: Our findings show the widespread exposure to BPA and DEHP and indicate that the exposure to BPA is significantly higher in obese girls. The frequent consumption of food packaged in plastic may be the main modality of BPA contamination. Further experimental and clinical investigations are necessary to unveil the potential cause-effect relationship.

P1-59**Growth patterns in non-syndromic childhood overweight: comparing children with early or late onset weight gain**

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Background: A rapid weight gain during infancy increases adult lean body mass, whereas weight gain during adiposity rebound at age 4-7 years results in increased adult fat mass and an increased risk of the metabolic syndrome and T2D. To understand the impact of age of obesity onset on growth, we classified non-syndromic childhood overweight into an early onset (EO, age 0-3) and a late onset (LO, age 3-7) group and characterized the growth patterns of the two.

Methods: The subjects were 1716 children (575 girls) of the GrowUp1974 Gothenburg cohort, of which 169 were overweight or obese at age 18 ($\text{BMI} > 25 \text{ kg/m}^2$). 64 children of the overweight group (28 girls) had a high BMI with an EO, age < 3 years, mostly before age 2y, and 105 children (30 girls), had a high BMI with a LO at average age 5.02y, (Chi-square for sexual dimorphism $p=0.044$).

Results: The adiposity rebound happened at comparable age. During childhood (age 1.5-3.5y; $p=0.050$) and juvenility (age 7-9y; $p=0.017$), and at age 18y ($p=0.041$), girls, but not boys of the EO group were taller and heavier ($p=0.046$), and their mothers were taller ($p=0.001$). The age at ICT (infant to childhood transition) and the age at the PHV (peak height velocity), indicating pubertal tempo, were comparable.

Conclusions: 1. The EO group had relatively more girls and they were more affected by obesity than the LO group. 2. During the entire growth period and at final height, girls of the EO group, and also their mothers, were taller than girls of the LO group. 3. The timing of onset of overweight can be used to distinguish between obese children who are likely (LO) or unlikely (EO) to embark on a trajectory, which leads to insulin resistance, the metabolic syndrome, and T2D.

P1-60**The effect of improved metabolic risk factors and metformin therapy on circulating hepatokines in obese, insulin-resistant adolescents**

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Introduction: The molecular mechanisms underlying insulin resistance (IR) is complex and has not been fully elucidated yet. The experimental studies point out the role of liver-derived proteins, called hepatokines.

Aims: To compare metabolic parameters and hepatokines levels in obese adolescents and healthy controls and to assess the effect of metformin therapy on plasma hepatokines levels in obese, insulin-resistant adolescents.

Material and Methods: Sixty-nine subjects (38 girls, 31 boys) aged between 12-18 years were included. Participants were categorized into two groups. The first-group comprised obese adolescents with a body mass index (BMI) $> 95^{\text{th}}$ percentile and the second-group comprised healthy controls with a BMI between the 5th and 85th percentile. Anthropometric and biochemical (glucose, insulin, lipid profile, Fetuin-A, fibroblast growth factor-21 (FGF-21), angiopoietin-related growth factor (AGF), leukocyte-derived chemotaxin 2 (LECT2) and Selenoprotein-P (SEPP1)) parameters were evaluated. Firstly, metabolic parameters and hepatokines levels were compared in obese group and healthy controls. Secondly all obese patients underwent a standard oral glucose tolerance test (OGTT). Patients diagnosed with IR at OGTT were started metformin (2g/day, 2 doses) therapy for 6-months. Then the differences in the biochemical characteristics and hepatokines levels analyzed between pre- and post-treatment. Plasma hepatokines levels were determined using an enzyme-linked immunosorbent assay (ELISA) method (Abbkine, Inc. China).

Results: Study included 44 obese (21 males, 23 females; mean age: 13.1 ± 1.9 years) and 25 healthy non-obese children (10 males, 15 females; mean age: 13.5 ± 1.9 years). Glucose, insulin, HbA1c, Fetuin-A, LECT2 and SEPP1 levels were significantly higher in obese patients ($p < 0.05$); FGF-21 and AGF levels were not significantly different between the two groups ($p=0.776$, $p=0.214$). There was a statistically significant decrease in serum glucose, insulin, HbA1c, total cholesterol, triglyceride and LECT2 levels and a statistically significant increase in serum HDL-cholesterol levels after 6-months of metformin therapy. There was no statistically significant difference in Fetuin-A, FGF-21, AGF and SEPP1 levels after treatment ($p > 0.05$).

Conclusion: Plasma levels of Fetuin-A, LECT2 and SEPP1, which are thought to be effective in insulin signaling pathways, were significantly higher in obese patients. Six-months of metformin therapy also found to be effective in decreasing serum LECT2 levels.

Keywords: Childhood-obesity, insulin resistance, metformin, hepatokines, fetuin-A, FGF21, AGF, LECT2, SEPP1

P1-61**Association among PGRN, HMGB1, and obesity related markers in young rat model of high fat diet-induced obesity**

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Objective: We aim to investigate the association among progranulin (PGRN), high-mobility group box 1 (HMGB1), and obesity related markers in young rat model of high fat diet-induced obesity.

Materials and Methods: 20 Male Sprague-Dawley (SD) rats at the age of 21 days were divided into two groups randomly. The rats were fed with normal diet (NC group) or high-fat diet (OB group). The NC group and OB group were sacrificed at the end of the forth week. The length, body weight, waist circumference (WC), liver weight, epididymal fat weight and Lee's index were measured or calculated. The serum level of ALT, AST, cholesterol, triglycerides (TG), high density lipoproteins (HDL), low density lipoproteins (LDL), fasting blood glucose (FBG), as well as fasting insulin (FINS) were measured, PGRN and HMGB1 in serum were detected by Elisa assay, while Western blot was used to detect the expression of PGRN and HMGB1 in liver and adipose tissue.

Results: The body weight, WC, liver weight, epididymal fat weight, and Lee's index of OB group were higher than those of NC group significantly ($P<0.05$). Hematoxylin and eosin (H&E) staining showed that rats in OB group displayed mild to severe hepatic steatosis, while those in NC group were normal. Compared with the NC group, the serum level of FPG, HOMA-IR, cholesterol, TG, LDL, ALT, AST in OB group is remarkable higher ($P<0.05$). The FINS were slight elevated in OB group than those in NC group. Elisa array showed that PGRN and HMGB1 were significantly increased in OB group compared with those in NC group ($P<0.05$). The correlation analysis indicated that PGRN had significant positive correlation with ALT, AST, TG, LDL and HMGB1 ($P<0.05$), while HMGB1 was positively correlated with ALT, AST, CHOL, TG, LDL and PGRN ($P<0.05$). Western blot demonstrated that compared with NC group, OB group had a higher expression of PGRN and HMGB1 in both of liver and adipose tissue ($P<0.05$).

Conclusions: PGRN, HMGB1 were associated with obesity and IR, They may be markers of obesity and related metabolism disease.

P1-62**Short-term treatment of liraglutide in patient with Prader-Willi syndrome**

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Background: Prader-Willi syndrome (PWS) is a genetic disorder associated with developmental delay, obesity, and

obsessive behavior related to food consumption. Treatment options for weight control in those patients is limited and there are controversies for a surgical approach. Saxenda® (liraglutide) injection 3 mg is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with obesity or overweight in the presence of at least one weight-related comorbid condition.

Objective: The objective of this study is to determine the effect of a 3-month trial of liraglutide on appetite, lipid profile, and weight in youth with PWS.

Methods: Three overweight and obese females with PWS (19-22 years) including maternal uniparental disomy (mUPD) were recruited for a 3-month open-label, non-randomized, longitudinal study conducted at Pusan National University Children's Hospital. Liraglutide was given using standard diabetes dosing without dietary modifications. Body Weight, body mass index (BMI), lipid profile, and appetite were measured over 3 months. Appetite scores was measured using the Dutch Eating Behavior Questionnaire for assessment of restrained, emotional and external eating behavior (DEBQ).

Results: Appetite scores was not significantly decreased from baseline and after 3 months of treatment (26.4 ± 6.8 and 26.1 ± 5.5 ; $p=0.84$). Hemoglobin A1c was not decreased after 3 months of treatment (6.63 ± 1.78 and 6.66 ± 1.81 ; $p=0.98$), but also weight, BMI z-score, and LDL-cholesterol did not (2.75 ± 2.03 and 2.81 ± 2.17 ; $p=0.97$, 3.79 ± 1.44 and 3.82 ± 1.59 ; $p=0.97$, 96.0 ± 52.0 and 103.6 ± 24.8 ; $p=0.82$, respectively). There was no significant change in waist circumference.

Conclusions: This is the first longitudinal investigation of the effects of liraglutide in subjects with mUPD PWS. It was not effective in decreasing appetite, without change in weight or BMI in the short term. Larger, controlled, longer-term trials in patients with PWS are required to confirm the efficacy and safety of liraglutide and to evaluate whether its use might induce weight loss when given in conjunction with behavioral modification.

P1-63**Altered gut microbiota in Obese children: sex-associated signature**

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Background: The incidence of obesity, especially in children, have dramatically increased over the last few decades. Recently, studies highlighted the involvement of gut microbiota in the pathophysiology of obesity. Gender-related differences have been reported in animal and adult. Nonetheless, reports related on the features of gut microbiota in children with obesity is limited and no one reported the different composition of gut microbiota at different sex of obese children.

Objective: The goal of this study is to analyze the differences of gut microbiota between obese and normal-weight children. In addition, to investigated the difference of gut microbiota in obese children with different sex.

Method: A cross-sectional study was performed between obese children and normal-weight children aged 6 to 14 years old who visited to Fuzhou Children's Hospital of Fujian Province from January 2018 to December 2018. The anthropometric and physiological parameters were obtained, and fecal samples were collected from all subjects. The relative abundance of gut bacteria was determined by 16S rRNA gene sequencing using Illumina MiSeq.

Result:

1) A total of 50 obese children (24 boys and 26 girls, mean age 9.67 ± 1.60 years, mean BMI 24.69 ± 1.96 kg/m²) and 24 normal-weight children (11 males and 13 females, mean age 9.08 ± 2.07 years, mean BMI 16.09 ± 1.91 kg/m²) were enrolled in this study. There was no significant difference in age between the two groups ($p > 0.05$).

2) There was no significant difference of alpha diversity between obese and normal-weight children ($P > 0.05$). Firmicutes and Bacteroidetes were the two predominant bacterial taxa in feces of the two groups. Linear discriminant analysis effect size (LEfSe) analysis showed that children with obesity were accompanied with a significant reduced abundance of Bacteroides (from phylum to genus), as well as an increased abundance of Enterococci (from order to family), Puccinia (from family to genus) and Escherichia compared to the normal-weight children ($P < 0.05$).

3) Characteristic microbiome in obese. Children with different sex showed that there was no significant difference in the alpha diversity of the gut microbiota between the two groups ($P > 0.05$); Also no significant difference at phylum level ($P > 0.05$) between the two groups. The genus level of Bilophila, Granulicatella, Lactobacillus, Megamonas, Paravotella and the species level of Bacteroides_ovatus and Bacteroides_uniformis in obese children with different sex were significant different between the two groups ($P < 0.05$).

Conclusion: Children with obesity exhibited a microbial flora which differed from those of normal weight and with a sex-specific responses.

16p11.2 copy number variants have shared phenotypic features (autism, developmental delay). Mirror phenotypes have also been described: deletions – obesity, hyperphagia, macrocephaly; duplications – underweight, feeding/eating disorders, microcephaly. Congenital anomalies, more common in duplications, have not had a predilection for a specific organ/system.

Two cases of 16p11.2 microdeletion syndrome that presented with diazoxide-responsive hyperinsulinaemic hypoglycaemia from the first weeks of life have recently been reported.(1)

To our knowledge, this is the first description of hyperinsulinaemic hypoglycaemia in a patient with 16p11.2 duplication syndrome.

Case: A full-term normosomic male born via assisted vaginal delivery due to failure to progress and foetal distress experienced neonatal hypoglycaemia requiring intravenous dextrose for 24 hours. Right grade IV vesicoureteric reflux and a bifid right collecting system was detected at 7 weeks. At 11 months he presented with hyperinsulinaemic hypoglycaemia during a gastrointestinal illness. He was diazoxide-responsive and at 8.5 years, continues at a dose of 6.5mg/kg/day.

His phenotype includes developmental delays, learning difficulties and anxiety, with diagnoses of Autistic Spectrum Disorder and Attention Deficit Hyperactivity Disorder. He has had low postnatal weight and BMI, with selective and restrictive eating behaviours. Cardiac surveillance due to diazoxide use identified a dilated aortic root (17 gene aortopathy panel negative).

Targeted next-generation sequencing of the coding regions and exon/intron boundaries of 16 genes (KCNJ11, ABCC8, AKT2, GLUD1, GCK, GPC3, HADH, HNF4A, INSR, KDM6A, KMT2D, SLC16A1, CACNA1D, PMM2, TRMT10A, HNF1A) in which mutations are reported to cause hyperinsulinaemic hypoglycaemia was performed. No pathogenic variants were identified.

Single nucleotide polymorphism (SNP) array detected a heterozygous interstitial duplication of approximately 551Kb (Chr16:29,647,342-30,198,151dup) at chromosome 16p11.2 containing at least 30 known genes confirming a diagnosis of chromosome 16p11.2 duplication syndrome. The duplication was not maternally inherited. Paternal DNA was not available.

Discussion: Our case expands the clinical spectrum of phenotypic abnormalities observed in the 16p11.2 duplication syndrome. The two reported cases of hyperinsulinaemic hypoglycaemia in 16p11.2 microdeletion syndrome were diagnosed neonatally and ceased Diazoxide within 15 months.(1) In one of these patients, it was postulated that SH2B1 deletion, associated with developmental delay, obesity and insulin resistance may have been contributory. However, in our case, SH2B1 was not within the duplicated region. Hence the biological mechanisms are unclear.

(1) Kostopoulou E *et al.* Clinical Endocrinology 2019

Fetal, Neonatal Endocrinology and Metabolism (to Include Hypoglycaemia)

P1-64

Hyperinsulinaemic Hypoglycaemia: A New Presentation of 16p11.2 Duplication Syndrome

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Introduction: *De novo* and inherited cases of 16p11.2 microdeletion and duplication syndromes have a spectrum of clinical manifestations, with incomplete penetrance and variable expressivity.

P1-65**Congenital Hyperinsulinism Due to Pancreatic Mosaicism for Paternal Uniparental Disomy of all Chromosome 11, with the Additional Finding of Pancreatic Mosaicism for Trisomy 12**

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We report a term male with diazoxide-unresponsive congenital hyperinsulinism (CHI) (spontaneous conception, non-consanguineous, no family history). The patient did not have macroglossia, exomphalos or lateralised overgrowth (cardinal Beckwith-Wiedemann spectrum (BWSp) features) (1). There was no polyhydramnios, macrosomia, facial naevus simplex, ear creases/pits, diastasis recti or nephromegaly/hepatomegaly (suggestive BWSp features) (1).

A targeted massively parallel sequencing (MPS) panel identified a heterozygous maternally-inherited ABCC8 variant (c.1332+4del) (minimal splicing effect predicted, classified as likely benign).

[¹⁸F]-DOPA PET/CT imaging had unexpected focal increased uptake in the pancreatic distal body and tail. Histopathology of subtotal pancreatectomy (day 22) showed focal adenomatous hyperplasia (trabeculae and islet nests composed of regular, oval or columnar cells; lacking atypia or conspicuous nuclear enlargement). Adjacent lobules had a relatively normal distribution of islets and exocrine acini. There was aberrant p57 expression in islet cytoplasm (nuclear in normal islets; negative in focal-CHI due to a paternal K_{ATP} mutation).

Within 2 weeks, medical support was again required with residual, increased [¹⁸F]-DOPA pancreatic uptake. A second resection (5% left in-situ) (day 36) achieved normoglycaemia.

At 21 months, he remains normoglycaemic with age-appropriate feeding (exocrine pancreatic supplements) and normal neurodevelopmental progress.

Aim: Extended genetic analyses in context of CHI, focal increased [¹⁸F]-DOPA PET/CT pancreatic uptake and atypical histology.

Methods: Pancreas (region of islet hyperplasia): (i) Targeted MPS hyperinsulinism panel with mosaic variant calling

programme on the sequence data (ii) Single-nucleotide polymorphism (SNP) array analysis. Peripheral blood and buccal cells: SNP array analysis.

Results: Pancreas: maternal likely benign ABCC8 variant was identified with a skewed allelic frequency; high level of paternal uniparental disomy (pUPD) (whole of chromosome 11); mosaicism for trisomy 12 (up to 50% of sample). Peripheral blood and buccal cells: no mosaic paternal uniparental disomy (pUPD) or trisomy 12 identified.

Conclusions: With 2 cardinal BWSp features (hyperinsulinism >1 week, escalating treatment; and pancreatic adenomatosis), the requirement of the international consensus statement for BWS clinical diagnosis is met (1). Placenta was not retained to assess size / mesenchymal dysplasia (1).

Chr11pUPD is the likely cause of hyperinsulinism. Pancreatic mosaic trisomy 12 is likely a coincidental finding and unrelated to the hyperinsulinism.

Even in the absence of overt overgrowth features, BWSp due to pUPD11 should be considered if (i) persistent, severe CHI without identified pathogenic K_{ATP} channel mutation(s) (ii) large focal pancreatic lesions (with/without a K_{ATP} mutation) or (iii) atypical histology.

(1) Brioude F *et al.* Nat Rev Endocrinol, 2018

P1-66**Diagnostical approach to adrenal failure in symptomatic preterm infants – Is saliva derived free cortisol the solution ?**

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Introduction: Newborn premature infants are susceptible to develop relative adrenal insufficiency (AI) following transition from fetal to extrauterine life. Clinical signs of AI include hypoglycemia, dysbalanced electrolytes, fatigue and low blood pressure. Collecting serum cortisol samples itself is stressful for the infant, which challenges - in addition to analytic problems due to interference between fetal, placental and maternal derived steroids - the interpretation of results. Saliva samples can be taken stressless and free cortisol can be measured excluding any analytical interference. However, the best diagnostic test for adrenal insufficiency in neonates has yet to be developed

Methods/ Objective: The aim of this study was (1) to assess the feasibility of obtaining sufficient saliva samples from preterm newborns to allow measurement of free cortisol by enzyme immunoassay and (2) to assess the correlation, if any, between salivary free cortisol and serum cortisol in preterm infants between 32+0 and 36+6 weeks' gestational age at birth, who showed clinical signs for adrenal insufficiency. Patients with diagnosed congenital adrenals hyperplasia were excluded.

Results: Samples for 118 paired serum cortisol and saliva free cortisol levels from 43 preterm infants were analyzed. (1) 93.5% of samples collected had sufficient salivary volumes for measurement. (2) Despite being statistically significant ($p < 0.0001$), the correlation (Spearman $r = 0.685$) between serum and salivary cortisol was not strong.

Discussion: Salivary free cortisol measurement is feasible but cannot be used to accurately reflect serum total cortisol. Further studies comparing salivary free cortisol to serum cortisol and establishing normative data for saliva derived free cortisol levels in preterm newborns are needed before salivary cortisol can be used for diagnostic routine purposes. Finding the diagnosis of preterm AI remains challenging

P1-67

Screening of congenital hypothyroidism using umbilical cord blood in a maternity hospital

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Background: Approximately one baby in 2000-3000 is born with congenital hypothyroidism (CHT). Newborn screening of CHT is conducted in different countries by the measurement of either thyroid stimulating hormone (TSH) or free thyroxine (FT4) or both. Whereas most Western countries screened CHT by using a blood spot collected on day 3 to 5 of life, some countries' programmes measure umbilical cord blood TSH or FT4 for the screening of CHT. In our maternity hospital, cord serum TSH concentration is routinely measured for all newborn babies, and FT4 is reflex-tested in the same cord serum specimen if cord TSH concentration is 23.0 mIU/L or above, or below 1.0 mIU/L.

Methodology: Umbilical cord serum TSH and FT4 concentrations were measured using automated immunoassays (Abbott Architect). Cord TSH (with or without FT4 results) generated from this screening programme between January 2016 and December 2017 (24 months) were retrospectively reviewed.

Results and Discussion: Within the 24-month period, 11130 females (47.9%) and 12127 males (52.1%) were screened for CHT. Cord TSH concentrations ranged from <0.01 to 482 mIU/L. Median TSH in males (4.91 mIU/L; IQR, 3.70 – 6.77 mIU/L) was slightly higher than median TSH in females (4.61 mIU/L; IQR, 3.47 – 6.28 mIU/L) ($p<0.0001$).

There were 22448 cord TSH results (96.5% of total) falling within the local TSH reference interval (2.20 – 24.99 mIU/L). Among those TSH results outside the local TSH reference interval, 742 results (3.2% of total) were below 2.20 mIU/L, whereas 67 results (0.3% of total) were 25.0 mIU/L or above. The vast majority of TSH results (88.6% of total) were between 2.20 and 9.99 mIU/L.

Approximately 0.5% of specimens underwent reflex measurement of free T4 concentration (when cord TSH concentration was 23.0 mIU/L or above, or below 1.0 mIU/L). The workload of FT4 reflex-testing is not considered onerous for laboratory resources. Among those 105 cord serum specimens with TSH concentration 23.0 mIU/L or above, their FT4 concentrations ranged from 9.0 to 20.6 pmol/L (local FT4 reference interval, 12.5 – 27.5 pmol/L). Median cord FT4 concentration was 12.7 pmol/L (IQR, 11.8 – 14.1 pmol/L) in newborn babies with cord TSH concentration 23.0 mIU/L or above. Correlation by linear regression both between FT4 and TSH concentrations and between FT4 and log(10) TSH concentrations was relatively weak (r^2 , 0.073 and 0.109 respectively).

P1-68

Growth and Cognition at peri-pubertal age in preterm infants very low birth weight: the role of extrauterine growth restriction (EUGR)

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Background: Preterm infants born VLBW can display auxological impairment and long term cognitive disabilities. These outcomes are influenced by the condition of being small for gestational age (SGA), but also by the extra-uterine growth restriction (EUGR). Aim of the study was to detect the influence of gestational age(GA), perinatal growth trend and enteral nutrition during the hospitalization on cognitive and auxological outcomes at peri-pubertal age (PPA).

Methods: Single center prospective study of VLBW discharged free from major disabilities or genetic diagnosis, which were evaluated through an auxological (growth parameters and pubertal stage) and cognitive assessment (Wechsler Intelligence Scale for Children IV-WISC-IV) between 10 and 13 years. Data are expressed as mean \pm SD.

Results: 40 VLBW (16M) entered the study. At birth, GA was 28,8(\pm 2,3) weeks and weight was 1035(\pm 257)g; 7 babies (17,5%) were SGA (6/7 born over 30 weeks GA). At discharge, 30 patients (75%) were EUGR, 95% of them born <27 or >30 weeks. Weight increase (WI) during the recovery was 17,4(\pm 4,1) g/die. 30% have been exclusively breastfed. Age at auxological and cognitive assessment was 11,5 (\pm 0,8) years. Height SDS (HSDS) for boys was 0,08 (\pm 1,17) and distance from target height (Δ TH) -0,228 (\pm 0,8), while for girls -0,14 (\pm 1,1) and 0,1 (\pm 0,9), respectively. BMI SDS was -0,19 (\pm 1,34) for boys and 0,5 (\pm 1) for girls. 13% of the whole population showed Δ TH >-1SD, 5,13% presented short stature (height<-2SD) and 48% had BMI<18. No pubertal disorders were found. VLBW who developed EUGR at discharge, showed significantly lower weight SDS ($p:0.03$) and BMI SDS ($p: 0.025$) at PPA. Patients who assumed breast milk from birth to discharge demonstrated an higher height SDS ($p:0.04$) than patients formula fed. WISC-IV assessment showed no minor or moderate cognitive disabilities but one patient, who scored mild mental delay. Neonates born between 27-30 weeks who did not develop EUGR had significantly higher scores in cognition at PPA (IRPQI $p:0.01$, total QI $p<0.01$). A WI > 18 g/die positively influenced the cognitive outcome at PPA (IRPQI $p<0.01$, total QI $p:0.02$).

Conclusion: An adequate growth in NICU during the first weeks of life may prevent EUGR of VLBWs and promote better growth and cognitive outcomes at PPA, independently from GA. A WI > 18 g/die promotes cognitive scores at PPA, while breastfeeding boost height growth at PPA.

Molecular mechanisms of Idiopathic Ketotic Hypoglycemia in children

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Idiopathic Ketotic Hypoglycemia (IKH) is the most common non-iatrogenic cause of hypoglycemia in children beyond infancy. The severity of the symptoms and frequency of hypoglycemic episodes may vary among the patients. The etiology of IKH is unclear; disturbances in gluconeogenesis, glycolysis and glycogenolysis were regarded as possible causes. Familial IKH recurrence is often observed, suggesting a genetic basis of glucose homeostasis dysregulation.

We aimed to investigate the possible molecular mechanisms of IKH condition.

Over the last 3 years, 114 children (48 females) were referred to the Endocrinology research center because of recurrent episodes of ketotic hypoglycemia. Investigations included measurements of serum glucose, liver transaminases, 3HOB, lactate, cortisol, insulin, pituitary hormones and acyl carnitine profile taken at the time of hypoglycemia (<3 mmol/l) and abdominal ultrasound. Additionally, genetic testing including ACAD9, ACADM, ACADS, ACADSB, ACADVL, ACAT1, AGL, AKT2, ALDOB, CPS1, CPT1A, CPT1B, CPT2, ETFA, ETFB, ETHE1, FBP1, G6PC, GBE1, GYS2, HADHA, HADHB, HMGCL, HMGCS2, HNF1A, INSR, MPI, MUT, NAGS, NPC1, NPC2, OTC, OXCT1, PCCA, PCCB, PCK1, PCK2, PDX1, PHKA2, PHKA2, PHKB, PHKG2, PPARG, PYGL, SLC22A5, SLC25A20, SLC37A4, and TANGO2 genes using the NGS technology has been carried out for 60 children.

The median age of hypoglycemia onset in our group was 4.75 y. The majority of patients had mild hypoglycemic symptoms such as irritability, confusion and dizziness. However, 26% presented with seizures and lethargy. 21 of 114 (18.4%) were diagnosed with pituitary hormones deficiency. Only 5 of 114 (4.4%) had biochemical abnormalities indicative for inborn metabolism errors, which were subsequently confirmed by genetic testing. It included fructose-1,6-bisphosphatase deficiency (n=1); 3-methylcrotonyl-CoA carboxylase deficiency (n=1); medium-chain acyl-CoA dehydrogenase deficiency (n=1); glycogenesis Ib (n=2). The rest 88 patients (37 females) were diagnosed with IKH. An NGS panel analysis was performed in 57 of them and revealed pathogenic hemizygous PHKA2 gene mutations in 4 children (7%). 18 patients were found to carry heterozygous pathogenic variants in following genes: PHKG2 (n=1); PHKB (n=2); OXCT1 (n=1); NCBI (n=1); INSR (n=2); HNF1A (n=1); GYS2 (n=1); FBP1 (n=1); ETFDH (n=1); CPS1 (n=1); ALDOB (n=1); AGL (n=1); ACADVL (n=2); ACADM (n=2).

To conclude: some cases of glycogen storage disease, especially its mild variants, may be misdiagnosed and labeled as IKH. Additional study is required to determine if some mutations are not detected because of the limitations of NGS method, or because the revealed heterozygous mutations in genes involved in glucose metabolism might be a predisposing factor for IKH development.

Congenital Hypothyroidism – Precise Diagnosis with Dual Imaging

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Introduction: Primary congenital hypothyroidism (PCH), defined as thyroid hormone deficiency, can be viewed as an anatomical, clinical, biochemical and radiological spectrum.

Its etiology includes thyroid dysgenesis (85%) with defects in thyroid gland development and thyroid dyshormonogenesis (15%) with inborn error of thyroxine synthesis or release.

There is growing evidence that precise characterization of thyroid dysfunction by dual imaging, scintigraphy and ultrasound (US) is helpful in improving both medical care and understanding of the underlying disease.

Scintigraphy is the gold standard method for assessing the diagnosis of ectopic thyroid tissue and color Doppler US can accurately measure the thyroid volume, reveal additional information regarding the anatomy of the gland and possible remnant of the thyroglossal duct.

We report 2 consecutive cases of PCH in which the dual imaging use allowed precise etiology.

Case presentation

Case 1. An 8-day-old female presented with prolonged jaundice and lethargy. Neonatal screening revealed a thyroid-stimulating hormone (TSH) level >100 µIU/mL. Repeat serum thyroid function tests, TSH >200 µIU/mL (0.20 – 4.20), thyroxine (T4) 1.8 pg/mL (7 - 17), triiodothyronine (T3) 0.4 pg/mL (0.9-1.95), thyroglobulin 500 µg/L (1.4 - 78), confirmed the primary hypothyroidism with both epiphysis absent on X-ray of the knee.

US scan of the neck was suspicious of thyroid agenesis and described a thyroglossal duct cyst. The nuclear scan (¹²³I) found an ectopic thyroid tissue in the wall of thyroglossal duct cyst. The wall of a thyroglossal duct cyst is the second most common site for ectopic thyroid.

Case 2. An 8-day-old male newborn presented with hypo activity. Neonatal screening was highly suggestive of congenital hypothyroidism. The report of TSH 50 mIU/mL, T4 4 pg/mL,

T3 1 pg/mL, and thyroglobulin 249 µg/L confirmed the diagnosis. X-ray of the knee showed normal ossification centers.

Neck ultrasound suggested hypoplasia of the thyroid tissue and described a thyroglossal duct cyst. ¹²³I scintigraphy yielded the final diagnosis of hemiagenesis, with absent left lobe.

Conclusion: Dual imaging allowed a specific diagnosis of the disorders of development of thyroid and abnormal obliteration of the thyroglossal duct. US and scintigraphy, as part of the optimal management of PCH, are complementary and provides the clinician maximal information on the anatomic and functional status of the thyroid. Parents can be counseled on either the certainty of lifetime treatment (dysplastic thyroid) or the possibility of later discontinuing therapy (eutopic thyroid). Neonatal thyroid imaging requires an extensive amount of experience.

P1-71

Clinical, biochemical and echocardiographic evaluation of patients with congenital rickets due to maternal vitamin D deficiency

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Objective: Vitamin deficient (VDD) rickets can manifest with skeletal (hypocalcemia, hypophosphatemia, elevated serum alkaline phosphatase and defective bone mineralization) and extra-skeletal findings. There are certain number of case reports and limited number of small scale studies reporting dilated cardiomyopathy due to VDD rickets.

The aim of the present study is to evaluate the clinical, biochemical and echocardiographic features of neonates with congenital rickets due to maternal vitamin D deficiency.

Patients and Methods: In this prospective cross-sectional observational study 148 neonates with the diagnosis of VDD rickets were recruited. Serum calcium, magnesium, albumin, phosphorus, alkaline phosphatase, parathyroid hormone (PTH), and 25(OH)D3 was measured. A low serum calcium elevated PTH and low 25(OH)D3 was defined as VDD rickets. Presentation at postnatal first month was considered as congenital rickets. Echocardiographic evaluation was performed to all patients. Echocardiographic measurement was assessed according to American Echocardiography Association Pediatric Echocardiography guideline. Vitamin D3 and oral calcium were administered to all patients, and a biochemical recovery was achieved in all. Following remission of clinical and biochemical VDD rickets, a control echocardiography was performed.

Results: The study included 148 cases (95 male). 119 out of 148 (80.4%) were presented at the first 72 hours. The presenting laboratory features for VDD rickets, echocardiographic parameters for evaluation of dilated cardiomyopathy at presentation and after treatment were shown in Table 1. In the echocardiographic evaluation, none of patients had dilated cardiomyopathy.

Conclusion: To the best of our knowledge, in this largest cohort of patients with congenital rickets due to maternal vitamin D deficiency, the echocardiographic evaluation did not show dilated cardiomyopathy in any of 148 cases, despite all presented with hypocalcemia and vitamin D deficiency. Absence of dilated cardiomyopathy can be attributed to early diagnosis and lack of prolonged exposure to the hypocalcemia. However, the exact underlying aetiology should be extensively investigated in all cases with dilated cardiomyopathy who presented with hypocalcemia and VDD rickets.

Table 1. Clinical and echocardiographic characteristics of cases

	Mean±SD (n=148)	Pre-treatment	Post-treatment	P value
Calcium (mg/dl)	7.1±0.5			
Phosphorous (mg/dl)	6.3±1.2			
ALP (U/L)	224.0±82.7			
PTH (pg/ml)	133.6.±79.5			
Mg (mg/dl)	1.8±0.2			
25(OH)D3 (ng/ml)	5.5±2.4			
Maternal 25(OH)D3 (ng/ml)	7.1±3.5			
EF (%)	69.3± 6.1	69.3± 6.1	70.6± 5.9	>0.05
SF (%)	37.8±4.3	37.8±4.3	38.2±4.0	>0.05
LVEDd (cm)	2.02±0.16	2.02±0.16	1.94±0.24	>0.05
LVESd (cm)	1.48±0.12	1.48±0.12	1.49±0.14	>0.05

GH and IGFs

P1-72

Diagnostic value of random serum growth hormone (GH), IGF-I and IGFBP-3 concentrations for the diagnosis of growth hormone deficiency (GHD) in patients below one year of life

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GHD diagnosis in neonates and infants is a challenge owing to the fact that GH pharmacological stimulation tests (GHST) are not approved at this age. In a retrospective study, we found that a random GH<6.5 µg/L confirmed GHD diagnosis in neonates with clinical suspicion of GHD with high diagnostic accuracy (1). The accuracy of GH and its surrogates of action have not been set for infants with current standardized immunoassays.

Objective: 1-To evaluate serum GH/IGF-I/IGFBP-3 concentrations in healthy neonates/infants in order to obtain normal reference intervals. 2-To investigate GH/IGF-I/IGFBP-3 usefulness for GHD diagnosis in infancy.

Design: Diagnostic validation study. Tertiary public hospital.

Methods: 430 healthy neonates/infants (2days-1year, 184 girls); 120 patients referred with clinical suspicion of GHD (2days-1year, 43 girls) from March 2015 to March 2019. Gold standard for GHD

diagnosis: growth retardation, other pituitary hormone deficiencies, brain MRI abnormalities or GHST during childhood. Infants in whom GHD was ruled out were diagnosed as having congenital hyperinsulinism (HI) or non-GHD. Reference values obtained in healthy neonate/infants were used to calculate SDS. Main outcomes by ROC were: sensitivity(S), specificity(Sp), negative predictive values(NPV) and area under the curve(AUC) of GH/IGF-I/IGFBP-3 (IMMULITE 2000XPi-Siemens).

Results: Controls: the highest GH and the lowest IGF-I and IGFBP-3 concentrations were found in 1st week old neonates. Thereafter, GH decreased and IGF-I/IGFBP-3 increased with age to reach the lowest GH and the highest IGF-I/IGFBP-3 concentrations beyond 6 months of age. GH and IGFBP-3 were always detectable in infants while 13% presented non-detectable IGF-I.

Patients: GHD was diagnosed in 41, HI in 24 and 56 were non-GHD. Only GH-SDS and IGF-I-SDS were significantly lower in GHD than non-GHD or HI ($p < 0.0001$). In infants, a GH cut-off of <-1.3 SDS presented: S: 0.94(0.74-0.99), Sp: 0.67(0.56-0.77), NPV: 0.98(0.90-1.0) and AUC: 0.90(0.83-0.95). IGF-I-SDS cutoff of <-1.1 SDS had: S: 0.73(0.58-0.85), Sp: 0.74(0.61-0.84), NPV: 0.79(0.68-0.89) and AUC: 0.75(0.67-0.84).

Conclusions: GH/IGF-I/IGFBP-3 concentrations should be weighed in the context of the clinical presentation and MRI findings. However, this study shows that GH constitutes a highly reliable biomarker for GHD screening in infants with clinical suspicion of GHD due to its high sensitivity and NPV. These data, in addition to our previous results on neonates, suggest that a random GH could be useful for GHD diagnosis throughout the entire first year of life.

(1)Ballerini et l. Horm Res Paediatr 2018

P1-73

Influence of birth parameters on growth response and metabolic effects of growth hormone (GH) therapy in GH-deficient children and adolescents

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Introduction: Growth depends on growth hormone (GH) secretion and on individual sensitivity to its action. The effects of birth parameters on growth and metabolic status are well documented in small-for-gestational-age children, but in children with GH deficiency those associations are not clear. Taking into account that GH-deficient children are not a homogenic group of patients, the importance of an individual approach to GH doses and the assessment of the effects of GH therapy is emphasised.

Aim of the study: We investigated the associations between birth weight (BW) and length (BL) and gestational age (GA) and anthropometric and biochemical parameters in GH-deficient children before and in the first year of GH therapy.

Material and methods: We analysed the data of 45 GH-deficient children (34 prepubertal, 11 pubertal) with mean BW -0.5 ± 1.02 SD and mean BL -0.6 ± 1.19 . BW and BL were expressed

as SDS for sex and GA. Height was expressed as SDS for chronological age, weight and BMI were expressed as SDS for height-age. Adiponectin, resistin, fasting glucose, fasting insulin, HOMA-IR, QUICKI, HbA1c, lipid profile, IGF-1 were analysed at baseline and during GH therapy.

Results: We found that BW correlated with baseline height SDS in prepubertal patients ($R = 0.38, p = 0.029$) and with height SDS after 12 months of GH therapy ($R = 0.73, p = 0.016$) in pubertal patients. GA was associated with both weight SDS and BMI SDS at baseline and after 6 and 12 months of GH therapy in prepubertal patients. Further analysis revealed that in prepubertal children GA was associated with adiponectin ($R = 0.39, p = 0.029$) and fasting glucose ($R = -0.45, p = 0.008$) at baseline and with resistin ($R = -0.49, p = 0.015$), IGF-1 SDS ($R = 0.44, p = 0.009$) and with increase in IGF-1 SDS ($R = 0.47, p = 0.018$) after the first 6 months of GH therapy. In pubertal patients we only found that baseline resistin was adversely associated with GA and BL ($R = -0.64, p = 0.035$; $R = -0.65, p = 0.031$, respectively). No correlations with insulin, HOMA-IR, QUICKI and lipid profile were found.

Conclusions: BW and GA seemed to be important factors affecting height deficit and nutritional status in GH-deficient children, especially before puberty. Higher GA is associated with better IGF-1 response to GH therapy, lower resistin and glucose levels at baseline and during GH therapy.

P1-74

Recombinant gh treatment in child with pseudopseudohypoparathyroidism associated with growth hormone deficiency

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Background: Pseudopseudohypoparathyroidism (PPHP) is a rare variant of pseudohypoparathyroidism (PHP) type I, with typical anatomical abnormalities known as Albright's hereditary osteodystrophy (AHO)(short stature, brachydactyly particularly involving metacarpals and metatarsals, round face, stocky build, ectopic ossifications and a number of possible associated defects), but with normal calcium, phosphate and PTH levels and normal response to exogenous PTH. Short stature results from a combination of multiple factors including the premature fusion of growth plates and absence of growth spurt in addition to GH deficiency. We report the case of a boy with PPHP and GHD, treated with rhGH to final height

Case presentation: A boy with morphologic features characteristic of AHO was followed in our Department because of severe growth retardation. He presented with a stocky build, mild obesity, round face and short neck, short pudgy hands, and feet with shortening and thickening of third and fourth metacarpals

and metatarsals, also demonstrated by radiological examination. Serum and urine calcium and phosphate levels were normal as well as serum ALP, PTH, and urinary cAMP concentrations. At the age of 9.5 years, he was diagnosed with isolated growth hormone deficiency demonstrating an abnormal GH response in standard provocation tests (peak GH 3.9ng/dl) and low IGF-1 levels. Since then the patient has been treated with rhGH for 6 years at a replacement dose (0.18–0.2mg/kg/wk). Even though in the beginning he presented a significant improvement of growth velocity (7.2 cm/y vs 3.5cm/y), the growth spurt during puberty was limited (22cm). As a result HSDS improved compared to pretreatment values (-1.93 vs -2.30), but final height reached the 3rd centile, far below the target height (50th centile).

Conclusion: To our knowledge this is the second case of a patient with PHPP and GHD treated with rhGH to final height. Similarly to the case of patients with PHP, it seems that rhGH treatment has a significant effect on growth in prepubertal years. Taking into account the limited clinically useful time window of effective treatment and the underlying skeletal disease, higher doses of rhGH should be considered in patients with PPHP.

Conclusion: The results suggest that -202 IGFBP-3 promoter polymorphism may not be a major factor in GH treatment in Korean children with ISS.

P1-76

The Diagnostic Value of Serum Acid-labile Subunit (ALS) alone and in combination with IGF-1 and IGFBP-3 in the diagnosis of Idiopathic Growth Hormone Deficiency (iGHD)

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P1-75

Impact of -202 IGFBP-3 Promoter Polymorphism on Growth Responses in Korean Children with Idiopathic Short Stature

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Purpose: Our previous study showed no correlation between -202 A/C IGFBP-3 promoter polymorphism and Δheight SDS in children with growth hormone deficiency. We investigated the influences of the -202 IGFBP-3 polymorphism on 1-year follow-up outcomes of GH treatment in Korean children with ISS.

Methods: Data was obtained from 81 children with idiopathic short stature (peak serum growth hormone (GH) \geq 7.0 ng/mL by GH stimulation test with 2 different stimulants). They were treated with GH for at least 1 year between 2014 and 2016. 69 of them were analyzed polymorphism of -202 IGFBP-3 promoter region (A or C). Their height velocity during GH treatment, serum insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) concentrations before and after GH treatment, respectively. Children with chronic disease, known syndromic disease and small for gestational age (SGA).

Results: Distribution of the -202 IGFBP-3 genotypes was as follows: AA genotype 69.6%; AC genotype 24.6%; and CC genotype 5.8%. Comparing the AA group with the AC and CC group, significant difference was observed in serum IGFBP-3 concentration at diagnosis ($P=0.032$) but no significant difference after the treatment ($P=0.499$). There were no statistically significant differences in ΔHeight, Δ IGF-1 level, and Δ IGFBP-3 level before and after GH treatment between two allele groups. No significant difference between C allele frequency and ΔHeight SDS was seen ($P=0.935$).

Background: The acid-labile subunit (ALS) is the crucial third player in the tertiary complex for its function of prolonging the half-life of the IGF1-IGFBP3 binary complexes. IGF1 and IGFBP3 are routinely determined during the diagnostic work-up for growth hormone deficiency (GHD). The aim of the study is to evaluate the relevance of serum ALS as an additional biomarker, alone or in combination with IGF1 and IGFBP3, in the diagnosis of GHD.

Methods: In a retrospective study, we had selected 91 children and adolescents (62 males) undergoing standard diagnostic work-up at the Department of Pediatrics and Adolescent Medicine of the Vienna General Hospital from 2010 and 2017. All patients met the inclusion criteria: short stature according to the SOP (height < -2.5 SDS, height deflection > 1 SDS, delta target height > 1.6 SDS), IGF1 and IGFBP3 lower as -2 SDS at first presentation, with at least one growth hormone stimulation tests and available baseline IGF1, IGFBP3 and ALS measurements. Excluded were pathologies that could explain short stature as well as those with no available baseline IGF1, IGFBP3 and ALS. Statistical analysis of different models consisting of ROC for various combinations of the measured parameters, as well as Odds ratio calculations were conducted using SAS software.

Results: 48 participants presented with GH values under 7 ng/ml and 43 above it. Mean IGF1, IGFBP3 and ALS were slightly lower in the participants with insufficient GH secretion. 4 participants with ALS levels < -2 SDS. The area under the ROC curve (AUC) from a model containing only IGF1 was 0.76, 0.68 when only ALS. A model containing both IGF1 and IGFBP3, (AUC=0.77) was unchanged if ALS is added as a second or third parameter (AUC=0.76, AUC=0.77). Furthermore, the variation in the outcome (GH-peak < / >= 7) explained by IGF1 only, amounts to 20.4% while that explained by IGFBP3 and ALS is only 10.6% and 7.8%. For IGF1, a -2 SDS cut-off delivers a sensitivity of 48% and a specificity of 83%. -1,5 SDS limit comes with similar sensitivity and specificity of 65%. For IGFBP-3, -2 SDS registered also an

extremely low sensitivity of 65%, by -1,5 SDS of only 53%. An ALS cut-off value of -2 SDS comes with a sensitivity between 8-10%. Sensitivity values above 80% were seen starting with -0,4 SDS, point where specificity is already under 50%.

Conclusion: Serum ALS measurement alone should not be used in the diagnostic work-up of short stature. Combining the measurement of ALS with IGF-I and IGFBP-3 does not improve the chances of diagnosing GHD.

Key words: IGF-1, IGFBP-3, ALS, Growth Hormone Deficiency

P1-77

Severe IGF-I deficiency in children with normal growth hormone (GH) secretion and excluded GH insensitivity – is it really idiopathic short stature?

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According to current recommendations, children with height SDS <-3.0, normal growth hormone (GH) peak in stimulation tests (stimGH) and severe IGF-I deficiency (IGFD) may be diagnosed with primary IGFD and treated with recombinant IGF-I. The need for direct confirmation of GH insensitivity is a matter of discussion. On the other hand, children born small for gestational age (SGA) with no catch-up growth are qualified to GH therapy despite normal GH secretion. The fact that some of them may fulfill the criteria of primary IGFD makes some confusion concerning the optimal treatment for them.

The aim of the study was to test the hypothesis that children with IGFD and excluded GH insensitivity may benefit during GH therapy despite normal stimGH and birth size appropriate for gestational age (AGA).

Retrospective analysis comprised 28 children (23 boys), age 13.0±2.2 years, including 6 cases of SGA and 22 of AGA, with height SDS <-3.0, stim GH >10.0 ng/ml and IGF-I SDS <-2.0, and with excluded GH insensitivity by significant IGF-I increase in generation test. The patients were treated with GH in standard doses for GHD up to final height (FH). The pre-treatment characteristics and the efficacy of treatment were compared between SGA and AGA.

There was no significant difference between AGA and SGA children in pre-treatment height SDS (-3.79±0.88 vs. -3.64±0.59, p=0.89), height velocity (HV) (3.8±0.8 vs. 3.4±1.0, p=0.34), stim GH (19.6±9.0 vs. 14.7±8.6 ng/ml, p=0.11) and IGF-I SDS (-3.08±0.98 vs. -2.60±0.39, p=0.37), as well as in IGF-I SDS at the end of generation test (-0.40±1.13 vs. -0.19±0.62, p=0.76). During 1st year of treatment, in AGA and SGA similar increase was observed for both HV (up to 8.6±3.3 vs. 7.2±2.2 cm/year, p=0.18) and IGF-I SDS (0.56±1.56 vs. 0.42±0.52, p=0.92). The attained FH SDS was even

better in AGA than in SGA (-1.66±0.94 vs. -1.82±0.87, p=0.53), similarly as the increase of FH SDS vs. pre-treatment height SDS (2.13±0.99 vs. 1.81±0.53, p=0.37).

It seems that children with height SDS <-3.0, normal stimGH and severe IGFD should not be diagnosed with primary IGFD if GH insensitivity is not documented. In case of AGA, they should not also be diagnosed with idiopathic short stature and remain untreated, as they may benefit during GH therapy at least similarly to SGA ones.

P1-78

Premature infants born small by gestational age: the role of insulin-like growth factor-1 in the regulation of postnatal growth

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The role of insulin-like growth factor-1 (IGF-1) in the regulation of growth of children with intrauterine growth is currently being discussed, but the final point of view has not been achieved.

Aim: to study the effect of IGF-1 in the dynamics of postnatal growth of premature infants with SGA in the first 5 years of life. Material and methods. The prospective study included prematurity with SGA (group 1, n=100) and prematurity corresponding to gestational age (group 2, n=69). Anthropometric (body length/height) and hormonal parameters (IGF-1) were evaluated at birth, at 1 year and at 5 years. Serum concentrations of IGF-1 were determined by immunochemiluminescence analysis. Statistical analysis was performed using the Mann-Whitney criterion of Spearman criterion.

Results: Premature infants with SGA naturally had lower body length at birth. Indicators of body length of prematurity in group 1 correspond 40.0 [35.5; 44.0] cm, in group 2 – 43.0 [40.5; 47.0] (p<0.05). In subsequent periods of follow-up, premature infants with SGA retained lower body length/height values: in 1 year - 71.5 [70.0; 73.4] cm (in group 2 - 75.0 [72.6; 76.0] cm, p<0.05), in 5 years - 104.5 [99.5; 108.5] cm (in group 2 - 108.0 [104.0; 110.5] cm, p<0.05). The concentration of IGF-1 less than 25.0 ng/ml in the neonatal period was observed in all examined groups 1. In group 2, the level of IGF-1 less than 25 ng/ml was registered in 25.0% of children, in 75.0% - there were fluctuations in the range of 27.1-78.0 ng/ml. Subsequently, the IGF-1 median was significantly lower in group 1. At the age of 1 year, IGF-1 values in group 1 were 63.3 [45.3; 77.8] ng/ml, in group 2 - 81.3 [66.3; 99.4] ng/ml (p<0.05); at the age of 5 years - 92.3 [56.9; 105.6] ng/ml and 134.0 [82.1; 168.0] ng/ml, respectively (p<0.05). The lowest values of IGF-1 were recorded in children of group 1 with severe growth retardation (less than -2.0 SD): in 1 year - 45.2 [41.3; 47.3] ng/ml (p<0.05), in 5 years - 43.0 [32.7; 49.7] ng/ml (p<0.05). Correlation analysis proved the relationship between growth retardation and the level of IGF-1 in the group of prematurely born with SGA: in 1 year r=0.72 (p<0.05), in 5 years – r=0.74 (p<0.05).

Summary: Insulin-like growth factor-1 in the first 5 years of life is one of the growth regulators of prematurity with SGA.

P1-79

The experience of pain in children with Growth Hormone deficiency and psychosocial correlates: preliminary data from a longitudinal prospective study

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Background: Pain represents one of the most stressful experiences for children undergoing medical therapies (Kortesluoma, 2008), but is under represented in literature for what concerns pediatric endocrinology. Children consider Injections one of the most painful, frightening and distressing procedures (Fassler, 1985). The treatment for patients with Growth Hormone Deficiency requires daily subcutaneous injection, performed by parents or patients themselves. This may represent a burden for family and have an impact on Quality of Life (QoL) (Brod et al., 2017; Bullinger et al., 2009). The present study aims to assess pain experience in pediatric patients undergoing GH therapy and explore psychosocial correlates.

Methods: 42 pediatric patients undergoing daily treatment with GH injections (males=61.5%, M age=11.8, SD=3.5) and one of their parents (mothers=73.1%) completed some questionnaire regarding QoL (QoLISSY, parent and child version), treatment burden (specifically designed questionnaire, parent and child version), emotional and behavioural characteristics of the child (CBCL, parent version). Also, a 7-day 0-10 points pain diary (Wong Baker Faces scale or VAS, based on age) was given to the family and returned to the researcher when completed, filled out by the patient after injection.

Results: Average pain score was 2.32, with younger children (3-10 years) experiencing significantly higher pain (M=3.04, SD=2.41) than older children (M=1.8, SD=1.07) [$p < .05$].

QoL was satisfying for 61.2% of patients and 46.6% of parents. A high number of participants described an insufficient QoL in all the considered sub-scales. In particular, "coping" scale was the most critical for patients (72.2% scored under cut-off) and parents (73.1%), who also reported issues in "beliefs" (65.4%) and "treatment" scales (88.5%).

Treatment burden for patients regarded the worry about forgetting to do the injection and their frequency, while parents reported feeling of sadness.

The 42.3% of parents described internalizing problems of their child (19.2% depressive symptoms; 11.5% somatic and social problems), while 11.2% reported externalising problems. Also, 23.1% of patients satisfied the DSM-IV criteria for Affective and Anxiety disorder.

Conclusions: These results highlight the presence of pain in young children in therapy for a GH deficiency, as well as a not satisfying situation for what concerns QoL and emotional/behavioural well-being, suggesting the need to pay attention to such issues in order to plan a better care of patients and families.

P1-80

Clinical characteristics, puberty pattern and adult or near-adult-height data in a group of patients with growth failure due to severe primary IGF-1 deficiency (GROWPATI study)

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Background: Severe primary insulin-growth factor-1 (IGF-1) deficiency (SPIGF1D) is a rare cause of growth retardation. Diagnostic criteria include age- and sex-dependent low basal IGF-1 levels (<2.5th percentile), height $\leq -3SDS$, absence of growth hormone deficiency and of any secondary causes of growth failure.

Objectives: Description of pubertal onset and growth spurt, data on adult or near-adult-height in a subgroup of patients diagnosed with growth retardation due to SPIGF1D.

Methods: Thirty patients (Male,M /Female,F:17/13) have been identified with SPIGF1D (historical study cohort) out of 2546 patients referred for growth failure to Paediatric Endocrinology Department of Necker Children's University Hospital, in Paris between 2004 and 2009 (Teissier et al, EJE, 2014). We extended this cohort including 19 more patients with SPIFGD characteristics (new cohort) among patients with growth retardation between 2016-2019. Data are presented for a subgroup of patients from both cohorts (n=19,11M/8F) concerning puberty (Tanner stage, menarche) and adult height, if available. Adult height was defined as last height velocity $<1\text{cm/year}$.

Results: From the current cohort of 49 patients with SPIGF1D, 29 patients were born small for gestational age (SGA). Genetic results available so far outline the heterogeneity of the disease: constitutional bone disease (skeletal dysplasia, n=4), hypochondroplasia (n=1), Laron syndrome (n=1), heterozygous GHR mutations (n=2), Noonan syndrome (n=1), Silver-Russell syndrome (n=2). Genetic studies are ongoing for the rest of the cohort. At inclusion all patients were pubertal stage 1. Mean actual age of patients in the historical and new cohort is 17 and

9.5 years respectively. Data are presented for the subgroup of 19 patients from both cohorts. Pubertal onset was normal with a mean age for Tanner stage 2 of 12.5 years for boys (n=11) and 12 years for girls (n=8). Mean age of menarche was 13.6 years with regular menstrual cycles. Two boys had advanced evolutive central puberty, treated by GnRH agonist. Adult height/near-adult height was available for 5 boys, mean (SD): -2.2 SDS(0.3) and 4 girls, -2 SDS(1), except a female patient with Laron syndrome (final height:128.5cm). Predicted adult heights for boys and girls with available final heights were -1.5 SDS(0.4) and -1.8 SDS(0.6), respectively. These patients have been treated by growth hormone or, for Laron syndrome, by Increlex®(recombinant human IGF1).

Conclusion: Final heights in our patients were below predicted adult heights, and height velocity during puberty varied. Long-term follow-up and genetic investigations are necessary for providing more insights in the SPIF1D.

P1-81

Effect of recombinant growth hormone therapy on retinal nerve fiber in children with idiopathic growth hormone deficiency

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Introduction: Growth hormone (hGH) and/or growth factors are thought to play a role in the pathogenesis of diabetic retinopathy. Increased treatment of human growth hormone (hGH) in children rise questions concerning the safety of GH replacement therapy on ophtalmic changes. Adverse effects of hGH treatment (pseudotumor cerebri, papilloedema, retinal changes mimicking diabetic retinopathy, neovascularization) have been reported in some papers. In this study, it was aimed to examine whether there is any change in retinal nerve fiber layer (RNFL) in long term during growth hormone treatment.

Material and methods: 10 patients with congenital idiopathic pituitary insufficiency (mean age, 13.1 year) were studied. Patients who had any disease or drug use that would affect the retinal nerve fiber layer, with any refractive error or additional ophthalmological problem were not included in the study. All patients underwent ophthalmic examination by same ophthalmologist at the beginning of the growth hormone treatment and after 6 month. Retinal nerve fiber layer of patients receiving treatment was evaluated by spectral domain optical coherence tomography.

Results: There was no change in the initial visual acuity, refraction, tension ocular measurements, anterior segment and fundus findings. The thickness values of 8 sectors in RNFL analyzes were recorded. There was no significant difference between the RNFL thicknesses of the right eye and left eye for 8 sectors before and after treatment.

Conclusions: It was found that recombinant growth hormone therapy did not cause a change in the retinal nerve fiber layer in children with idiopathic growth hormone deficiency. There was no adverse effect on the RNFL.

P1-82

Positive impact on adherence through educational activities of the Argentina's Patient Support Program in children with low adherence to treatment with recombinant Growth Hormone (easypod applicator)

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Background: One of the main concerns in patients with growth disorders is to achieve optimal adherence to growth hormone (GH) treatment. For this it is important to identify patients with low adherence to treatment and to evaluate actions to improve it.

The Merck Patient Support Program (PSP) carried out educational actions aimed at patients with low adherence and their parents, to raise their awareness of the importance of good adherence in achieving adequate efficacy. In this study, our objective was to measure the effect of one these actions and its direct impact on the patient adherence.

Methods: This was a 12-month observational, retrospective cohort study. Adherence rate data were collected from the PSP database from April to September 2015. Patients with low adherence (<80%) who were visited after the educational visit were selected. Their adherence was measured over 6 months, before and after the educational visit.

Patient demographic data were tabulated and graphed. Statistical analyzes were carried out with the STATA 15.0 software.

Continuous variables were presented as mean and median with their respective 95% CI and categorical variables were presented as proportion with 95% CI. For an adherence comparison the "Wilcoxon sign-rank test" test was used. A multivariable linear regression was performed to assess which independent variables contribute to the variability of adherence in this population and p<0.05 was considered significant.

Results: Data from 80 patients with low adherence were analyzed. Gender distribution was 65% male, 35% female. Patients were aged between 2–18 years (mean: 11.77). The diagnoses were: Growth Hormone Deficiency 71.25%, Small for Gestational Age 20%, Turner Syndrome 7.50% and Chronic Renal Disease 1.25%. Duration of treatment was 0.4–11.13 years (mean: 4.34).

At baseline, median adherence was 67% and after the intervention it increased to 76%, a statistically significant median improvement of 9% (p=0.0000 Wilcoxon sign-rank test). Also 34% (29/80) of the patients increased their adherence to values considered as good adherence ($\geq 80\%$). Both changes were clinically relevant.

No significant variables were observed in the regression model for this population.

Conclusions: Low adherence to GH therapy is multifactorial and there are few effective methods to improve adherence. We conclude that "the educational intervention" is a simple and low-cost method to improve adherence rate in patients with low adherence and recommend this type of action in these patients to reduce the gap between the indication / recommendation of the specialist and the patients' behavior.

P1-83

Identification of novel recessive *IGFALS* mutations and *INSR* variant in an obese Korean boy

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IGFALS gene is located in chromosome 16p13.3 encoding acid labile subunit which binds insulin-like growth factors (IGFs) to increase their half-life and vascular localization. The biallelic defect of this gene leads to acid-labile subunit deficiency characterized by postnatal growth retardation, insulin resistance, delayed puberty, and no growth hormone deficiency. A 5-year-old-boy was referred to as low IGF-1 and cortisol level. He presented with obesity and growth retardation. This subject was born in 36 weeks and 6 days with 2.04 kg of birth weight. The height, weight, and body mass index were 104.7cm (-1.0 standard deviation score, SDS), 29.7kg (2.9 SDS), and 27.1 kg/m² (3.2 SDS), respectively. He had acanthosis nigricans on neck, axillary, and inguinal area. He had severe obesity, obstructive severe sleep apnea, and heavy snoring and picking habitus were observed. Laboratory finding showed severely low levels of IGF-1 (4.55 ng/mL) and IGFBP3 (<500 ng/mL). Morning fasting glucose, insulin and glucose level was 3.9 ug/dL, 91.49 uIU/mL and 99 mg/dL. We performed methylation test for 15q11-12 Prader-Willi syndrome chromosome region and pituitary function test. All results were normal. His growth hormone peak provoked by hypoglycemia and L-dopa administration was normal (17.9 ng/mL and 7.36 ng/mL). The targeted exome sequencing for growth hormone resistance syndrome was done in this subject and the result revealed novel biallelic mutations, c.680C>A (p.Ala227Glu) and c.1897C>T (p.Arg633Trp), in *IGFALS* gene. Each mutation was inherited from his mother and father, respectively. We found an additional rare variant, c.1517G>A (p.Arg506Gln) in *INSR* gene. Here in, we report a Korean boy with novel compound mutations of *IGFALS* and likely pathogenic variant of *INSR* presenting with growth retardation, acanthosis nigricans, and severe obesity. The long-term effect of IGFs dysfunction on glucose metabolism, growth, puberty, and obesity in this subject should carefully be follow-up and we will assess the effectiveness of growth hormone.

Growth and Syndromes (to Include Turner Syndrome)

P1-84

Development of a parent experience measure for parents of children with achondroplasia

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Background: Limited research exists on how having a child with achondroplasia impacts parents' daily lives and well-being.

The purpose of the study was to gather qualitative evidence to support the development of a parent experience measure that assess the impacts of having a child aged 2 to <12 years with achondroplasia.

Methods: Concept elicitation interviews via individual telephone calls and an in-person focus group were conducted with parents of children with achondroplasia (aged 2 to <12 years) in the United States (US) and Spain using a semi-structured interview guide to elicit parents' experiences. Based on an adapted grounded theory approach, interview transcripts were analyzed to identify important themes and impacts for the development of a validation-ready parent experience measure.

Results: Thirty-six parents (n=31 mothers; n=5 fathers) of children with achondroplasia participated in individual interviews or the focus group (Spain, n=11; US, n=25), including seven parents with achondroplasia. Analyses identified four key domains relevant to the daily lives and well-being of parents of children with achondroplasia, including emotional well-being, caretaking responsibilities, family life, and work. In the parent emotional well-being domain, the most frequent impacts were worry about child's future (75%, n=27), worry about child's physical health (67%, n=24), concerns about child's safety (50%, n=18), feeling stressed/overwhelmed (44%, n=16), worry about child's social well-being (42%, n=15), and worry about child functioning independently (33%, n=12). For caretaking responsibilities, the most frequent impacts were managing child's medical care (e.g., appointments, treatment decisions; 92%, n=33), helping child with self-care (e.g., toileting, bathing, dressing; 67%, n=24), advocating for child (e.g., for school accommodations; 64%, n=23), providing assistance to child (e.g., reaching objects; 56%, n=20), monitoring child (e.g., to ensure safety or monitor health conditions; 47%, n=17), and providing support or guidance for child regarding living with or managing achondroplasia (47%, n=17). For the family life domain, the most frequent impacts included family strain (56%, n=20), family vacations/travel (53%, n=19), and family activities (42%, n=15). In the work domain, the most frequent impact was missed work time (e.g., for doctor appointments; 50%, n=18).

Conclusion: The findings provide evidence for content validity of the parent experience measure for parents of children with achondroplasia aged 2 to <12 years. To fully evaluate the value of new treatments for achondroplasia, it is important to understand and assess impacts on parents' daily lives and well-being, which may be lessened following children's treatment.

P1-85

Bone mineral density is normal in prepubertal patients with turner syndrome when corrected by height/age

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Introduction: Turner's syndrome (TS) is associated with several manifestations the most frequent being short stature and

hypogonadism. Some authors (Nadeem, 2012; Bakalov, 2008) reported that individuals with TS have increased risk of fractures, but the etiology and mechanism of bone fragility have not been yet fully elucidated and may be exacerbated by hormonal factors (Cintron, 2017; Soucek, 2015). Bone densitometry (BD) through the emission of double energy X radiation (DXA) is used to evaluate bone mineral content, but it analyzes only a two-dimensional measure of the bone and not its real volume. It is the most widely used method in the world to predict the risk of fractures (9). The interpretation of the BD in children should be performed by means of Z-score and, for individuals with short stature, it is recommended to adjust the values for bone age or for height/age (Brandao, 2009; Zerbini, 2006).

Objectives: To describe bone density at the lumbar spine (LS aBD) in a group of prepubertal TS individuals and compare the result after height/age correction.

Method: Retrospective analysis of medical records of healthy TS girls who had never received rhGH, anabolic steroids or estrogens. The variables analyzed were: karyotype, age at BD, weight, stature, body mass index (BMI) and BD (DEXA) result. We performed the adjusting of the BD result using the height/age (HA). Statistical analyses of the data were performed using SPSS software. The Wilcoxon test was used to compare the BD and BD-HA results; the Mann-Whitney test was used to compare the distribution of BDs in relation to karyotype and BMI; for the calculation of the probabilities was used the bootstrap technique, Monte Carlo method. The significance level of 5% ($\alpha=0.05$) was used. The study was approved by the institutional Ethics Committee.

Results: 37 prepubertal girls were identified, 13 were selected after exclusion criteria. They were aged between 10-13 years-old. Regarding the BD study, a mean (SDS) of -1.62 (1.32) ranged between -3.90 and 0.70 was found. The result after adjusting for height/age showed a significant difference with a mean of 0.39 (1.18) [-2.0 to 2.40], and no differences according karyotype and adiposity.

Conclusion: Prepubertal TS girls had normal bone density when adjusted for height/age, without influence of karyotype and BMI. Lower BD values are associated with the short stature bias, and when the results are adjusting for height/age, the values are within normal limits.

P1-86

Extreme short stature and poor pubertal growth: when *FBN1* is the culprit

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Introduction: Very short stature is a common presenting complain that gives rise to numerous investigations. *FBN1* heterozygous mutations cause acromelic dysplasia syndromes. The phenotypic spectrum of these growth disorders is broad, ranging from short stature with short extremities, stiff joints, skin thickening with tracheal stenosis and cardiac valvulopathy to nearly isolated short stature. Here, we report on a girl with disproportionate short stature, a history of small birth length, aortic bicuspidity and learning difficulties that harbours a previously described *FBN1* mutation.

Case Report: A 3.5y-old girl presented for short stature. Her parents were healthy, non-consanguineous, of Caucasian origin. Their height was 175,6 cm (father) and 166,8 cm (mother). She was born at 37 weeks of gestational age by caesarean section after a twin pregnancy obtained by IVF with 1900g and 44,5 cm. Her physical examination at 3.5 years revealed short stature (Height -3.1 SDS, ref Cole 1995), with relative macrocephaly (head circumference 0SDS), lumbar hyperlordosis. Parents repeatedly reported behavioural and learning difficulties. She also presented bicuspid aortic valve asymptomatic Arnold Chiari 1 associated with minor syringomyelia. Growth hormone was administered at 4.9y when her height was at -3.5 SDS with a bone age equal to chronological age. It was given for 18 months at a dose of 25 mcg/kg/d (height gain after 1 year: +0.4 SD) then stopped for 1 year (loss of 0,4 SD) and then restarted at a dose of 50 mcg/kg/d for 36 months (gain of 0,5 SD after 2 years). She started puberty at 10.3 years of age and 122 cm (-3SDS) and a bone age of 10 years (G and P). She had her menarche at 12.7 years of age and 132.1cm. Her final height is 133.5 cm (-5,1 SDS) with an arm span of 133cm, head circumference of 58 cm (+2.5 SDS), sittingHeight/Height = 0.56. Her diagnostic work-up included: repeated growth hormone stimulation tests, skeletal survey, caryotype with FISH for SHOX, microarray, PTPN11 and FGFR3 sequencing, 3M syndrome suspicion (bone dysplasia clinic advice). At 13,5 years of age, targeted exome sequencing showed a c.5183C>T (p.Ala1728Val) heterozygous mutation in the *FBN1* gene.

Conclusion: We highlight the very poor pubertal growth and very short adult height of this patient with acromicric dysplasia due to a *FBN1* mutation. In addition, we illustrate the diagnostic challenge for which targeted exome sequencing was of great help. Finally, Growth hormone therapy response was very poor.

Long-term safety follow-up after Omnitrope® (recombinant human growth hormone) treatment in short children born small for gestational age (SGA): latest results

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Background: The benefit of recombinant human growth hormone (rhGH) in improving height is widely recognised; however, rhGH therapy can affect carbohydrate metabolism and lead to impaired glucose tolerance during treatment. In addition, short children born SGA are predisposed to metabolic abnormalities. This study assessed the long-term safety of growth hormone (Omnitrope®) use in short children born SGA for up to 10 years after the end of treatment.

Methods: Conducted between June 2009 and October 2018, this was a follow-up observational study of patients from a phase IV study. All patients who participated in the phase IV study and received at least one dose of study medication were invited to enter a safety follow-up period of up to 10 years. The baseline visit was the final visit of the phase IV study. Further visits were planned after 6 months (F1), 1 year (F2), 5 years (F3) and 10 years (F4). The primary objective was to evaluate the long-term effect of rhGH treatment on the development of diabetes mellitus; secondary objectives included incidence/severity of adverse events (AEs).

Results: In total, 130 subjects were enrolled in the follow-up study; 99 completed F1, 88 completed F2 and 13 completed F3 (no subject reached F4). The full analysis set for evaluation comprised 118 patients (64 female). Mean (SD) age at baseline was 14.79 (2.85) years, mean weight was 44.97 (13.34) kg and mean (SD) BMI SDS was -0.84 (1.37). Mean (SD) duration of follow-up was 39.6 (24.4) months. No subject was newly diagnosed with diabetes. The results for carbohydrate metabolism parameters were consistent with this finding. A total of 144 AEs were reported in 54 subjects; these were mostly of mild-to-moderate intensity (96.5%) and not suspected to be related to previous rhGH treatment (94.4%). Serious AEs (n=18) have been reported in 8 patients; 3 (in 1 patient) were suspected as possibly related to previous rhGH treatment (anemia, menorrhagia, oligomenorrhea). One fatal event occurred (sepsis), which was judged as not related to previous rhGH treatment.

Conclusions: None of the participating subjects, who had all been previously treated with Omnitrope® in a phase IV study, developed diabetes during this follow-up study. In addition, no other unexpected or concerning safety signals were observed.

Etiology of Severe Short Stature: Single Center Experience

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Background: Based on growth screening rules, severe short stature (*i.e.* height SDS less than -3), at the age of more than 3 years, warrants diagnostic evaluation in specialized health care. In the absence of apparent underlying cause, targeted and eventually untargeted genetic studies have been proposed. However, the etiology of short stature at the severe end of the spectrum is poorly characterized.

Methods: We identified all subjects with height SDS < -3, after the age of three years, from our hospital district (Helsinki University Central Hospital, population of 1.2 million) growth database. Subjects with erroneous or missing data, born prior to 1990, or place of residence outside the hospital district were excluded. Total of 821 subjects (394 females, 427 males) fulfilled our inclusion criteria; we reviewed their medical records, growth data (22129 height measurements), and report their underlying diagnoses.

Results: A pathological cause for short stature (*i.e.* condition other than ISS) was diagnosed in and 287 (73 %) girls and 284 (67 %) boys (P=NS). The five most frequent causes in girls and boys were syndromes (26 % vs. 13%, P<0.001), ISS (23 % vs. 30 %, P<0.05), disorders in organ systems (15 % vs. 16 %, P=NS), SGA without catch-up growth (9 % in both sexes), and defects in the GH-IGF-I system (8 % vs. 14%, P<0.01). The probability of growth-related pathology was increased with the deviation from the target height, and with the shorter SD score. For example, in patients with the shortest measured height <- 4 SDS, skeletal dysplasia or a syndromic cause was identified in half of the cases, whereas ISS was rare (<7%).

Conclusions: By applying the cut-off of -3 SDS after the age of three years, severe short stature was equally frequent in girls and boys, and pathological causes were found in more than two-thirds in both sexes. Pathological causes were particularly frequent in the shortest subjects and in those with higher target height. Given that our hospital serves as the primary referral center for the region's well-child and school primary health care services, our results are expected to represent the spectrum of growth disorders at the population level.

P1-89

Clinical Outcomes in Primary Empty Sella (ES) Syndrome in Childhood-Onset Growth Hormone Deficiency: Data from KIGS (Pfizer International Growth Database)

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Background: The incidence of ES in children varies greatly depending on the population surveyed, ranging from 1.2%-9% to 68% (children without and with known endocrinopathies, respectively). MRI is the main diagnostic tool for screening pituitary and in a previous KIGS study, 3.0% of patients with GHD were identified with ES and 7.8% with pituitary hypoplasia (Maghnie *et al*, EJE (2013)).

Aim: To evaluate the clinical outcomes to GH treatment in patients with ES and compare the clinical response in patients with pituitary hypoplasia (PH), hypoplastic anterior pituitary, missing stalk and ectopic posterior pituitary (HME) and other central malformation (OCM).

Patients and Methods: All patients diagnosed with GHD and neuroimaging findings of ES, PH, HME and OCM in KIGS were included in this study. Descriptive statistics for the ES cohort compared growth response to GH treatment at yr 1, 5 and near adult height (NAH). Delta height SDS (Δ Ht SDS) among the other cohorts were compared at yr1. Wilcoxon signed rank and Kruskal-Wallis tests were applied. Significance level=5%.

Results: Clinical characteristics and outcomes in patients with ES.

Conclusion: A significant clinical response to GH treatment in ES patients was observed at all treatment time points. Patients with other diagnosis also demonstrated a positive response to treatment at year 1.

P1-90

Quality of life in caregivers of young children with Prader-Willi syndrome

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Objective: This study was to measure quality of life (QOL) of the primary caregivers for young children with Prader-Willi syndrome (PWS).

Methods: The children with PWS consisted of 32 children. The QOL of the caregiver for each patient was assessed using the Chinese version of the WHOQOL-BREF, and the Infants-Junior Middle School Students' Social-Life Abilities Scale was used to evaluate the social adaption capacity of the children. In addition, the data of children' profile and caregivers' characteristics were collected. Correlation test was used to explore the related factors to caregivers' QOL.

Results: QOL in caregivers of young children with PWS was lower than healthy norms. Risk factors of child's age, children with combined diseases or symptoms, caregivers having concerns about the child and poor social adaption of the child were associated with caregivers' QOL identified by Pearson or Spearman correlation test.

At visit	Baseline	Yr 1	Yr 5	NAH	P-value**
Variable	Mean (SD)	Mean SD)	Mean SD)	Mean(SD)	
N (boys %)	702 (69)	702 (69)	370 (69)	89 (61)	
Age at diagnosis (yr)	7.7 (5.0)				
Chronological age	8.0 (4.9)	9.0 (4.9)	11.3 (4.1)	17.6 (1.4)	<.001
Mid-parental Ht SDS Prader	-0.8 (1.2)				
Height (SDS) Prader	-3.5 (1.6)	-2.5 (1.5)	-1.1 (1.4)	-0.8 (1.3)	<.001
Δ Ht SDS Prader		1.0 (0.8)	2.5 (1.4)	3.1 (1.5)	<.001
Ht - MPH (SDS) Prader	-2.6 (1.6)	-1.6 (1.4)	-0.3 (1.4)	0.1 (1.1)	<.001
Weight (SDS)	-2.4 (2.0)	-1.7 (1.7)	-0.4 (1.6)	-0.3 (1.9)	<.001
In puberty	11%	20%	37%	100%	
Bone Age (yr)	6.2 (4.1)	7.3 (4.3)	10.0 (3.6)	15.8 (1.4)*	0.031
Max GH peak (μ g/L)	4.6 (5.7)				
Dose (mg/kg/week)	0.22 (0.08)	0.21 (0.06)	0.20 (0.06)	0.15 (0.09)	<.001
Years on GH treatment				10.6 (3.6)	

*N=13 at NAH; **Comparing NAH vs baseline

Summary results for other cohorts included height SDS at baseline and year 1 Δ Ht SDS: PH (n=180; -3.4(1.6); 0.9(0.7), HME (n=485; -3.3(1.7); 1.1 (1.0) and OCM (n=121; -3.5(1.6); 1.0(1.0). P-values=0.09, 0.134. No new safety signals were reported.

Conclusion: When the treatment plan is made for the patients with PWS, caregivers' supports are taken into consideration, especially for those who care the children with age of less than 6 years old.

P1-91

Ectopic posterior pituitary, polydactyly, midfacial hypoplasia and panhypopituitarism due to a novel heterozygous IVS11-2AC(c.1957-2AC) mutation in GLI2 gene

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Objective: Glioblastoma 2 (encoded by *GLI 2 gene*), is an activating zinc-finger transcription factor, involved in the Sonic Hedgehog pathway and embryogenesis of diencephalon and distal extremities. Heterozygous mutations of *GLI2* gene cause a wide range of clinical phenotype known as holoprosencephaly and holoprosencephaly-like syndrome, pituitary insufficiency, mid-facial hypoplasia, and polydactyly. We, herein, report a novel heterozygous IVS11-2A>C(c.1957-2A>C) mutation in *GLI2* gene with an extremely distinct phenotypical expression in two siblings and their father from an unrelated family.

Cases Reports: The index case is a boy who was born after 40 weeks uneventful gestation via spontaneous vaginal delivery. His birth weight was 3700 gr. He has developed cholestasis on the first postnatal day. Etiological investigations including metabolic screening as well as liver "tru-cut" biopsy were normal. During follow-up, he presented with hypoglycaemia episodes. In physical examination he had postaxial polydactyly, mid-facial hypoplasia, high palatal arch, micropenis, bilateral cryptorchidism and a diagnosis of multiple pituitary hormone deficiency (MPHD; ACTH, TSH and GH) was considered. In pituitary MR imaging he had ectopic posterior pituitary with no other structural abnormality. An orchioepexy performed. Na-L-Thyroxin, hydrocortisone and GH replacement therapies commenced. At his recent follow up visit his height was 133.5 cm (-0.46), weight was 28.7kg (-0.51 SD) and body mass index was 16.1 kg/m² (-0.4 SD). On physical examination, he had bilateral postaxial polydactyly, mid-facial hypoplasia, high palatal arch and moderate mental retardation. He was on antiepileptic therapy for focal epileptic seizures. In molecular genetics analysis, a novel heterozygous IVS11-2A>C (c.1957-2A>C) mutation detected in *GLI2* gene. His father and 6 year-old brother also had the identical heterozygous mutation with an incomplete phenotypical expression. Of which both had only postaxial polydactyly with no any hormonal deficiency or additional clinical finding. The apparently healthy mother and 4 years-old sister were negative for the mutation.

Conclusion: Extrapituitary findings accompany MPHD may provide clues for the diagnosis of particular gene mutations such as *GLI2*, *HESX1*, *LHX4*, *SOX3*, and *OTX2*. Present novel heterozygous mutation detected in the *GLI2* gene suggested an extremely variable clinical phenotype in individuals with identical mutation, even in those within the same family and incomplete penetrance of this gene mutations. Therefore, being aware of the association of extrapituitary manifestations like holoprosencephaly, ectopic posterior pituitary, polydactyly and midfacial hypoplasia with MPHD would provide a prompt diagnosis and proper management of cases with the *GLI2* gene mutation.

P1-92

A rare case of pseudoisodicentric X chromosome in a patient with primary amenorrhoea

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Background: Pseudoisodicentric X chromosomes with an Xq deletion (46,X,idic(Xq)) are rare. Most cases are mosaic, the other cell line being 45,X. Nonmosaicism is rare. Phenotype is characterized by the resultant of the X deletion. Variations from short to tall stature can occur and premature ovarian failure is a common feature.

Case Presentation: A 16 year old girl was referred to our clinic with primary amenorrhoea. She was also known with learning disabilities. Physical examination showed a normal height (+0.8 SDS) and minimal pubertal development (A1, P2, M1-2). Laboratory testing demonstrated hypergonadotrophic hypogonadism: FSH 62,8 U/L; LH 19,4 U/L; estradiol <0,06 nmol/L; and progesterone <0,6 nmol/L.

Results: Conventional karyotyping of lymphocytes repeatedly revealed an aberrant X chromosome consisting of twice the short arm, twice a centromere and twice the long arm until Xq27, with a loss of a small part of the long arm of the X chromosome (non-mosaic 46,X,psu idic (X) (q27)). Genomic micro-array showed duplication of Xp22.33q27,1 and deletion of Xq27,1q28.

Conclusion: The deletion of only a small part of Xq supports the 'inactivation' hypothesis, which means that a larger deletion of the long arm of the X chromosome leads to a larger part of inactivation of that X chromosome. Consequently, the two short stature-homeobox (*SHOX*) genes located in the region of Xp present on the aberrant chromosome are inactivated. The exact mechanism behind this theory remains to be discovered. In our patient, the deletion of Xq is small. This small deletion did not inactivate the *SHOX* genes, explaining the normal stature. Xq26 - q27 is critical for ovarian functioning, as reported in literature. Deletion of Xq27 in our patient caused premature ovarian failure and as a consequence hypergonadotrophic hypogonadism.

Persisting Embryonal Infundibular Recess in a patient with Morning Glory Syndrome and multiple pituitary deficiencies

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A 5-year old boy was referred to our clinic for short stature reported since first years of life. At birth weight and length were normal, psychomotor development was regular, target height was 165.9 cm. At 7 months of life he was subjected to correction of cleft lip-palate. Since 3 years of life he suffered from headache, for which a fundoscopy was performed and revealed a Morning Glory Disc Anomaly (MGDA) of the right eye. At our first visit height was 98.2 cm (-2.5DS), body proportions were regular, IGF1 levels were low, bone age was delayed (3 years and 8/10). Stimulation test for GH secretion revealed a GH deficiency (arginine peak 2.2 ng/ml, glucagon peak 6.9 ng/ml). MR imaging showed hypophyseal hypoplasia and a stubby, thickened, and inferiorly dropped optic chiasm with normal signal intensity. In sagittal images was also noted a dysmorphic hypothalamic infundibulum and pituitary stalk. An interesting finding was a direct communication between the third ventricle and the sellar cavity, suggesting a Persisting Embryonal Infundibular Recess (PEIR), the absence of sphenoidal meningocele was carefully proven. The sella was mildly enlarged, clival hypoplasia was noted. Additional findings were: a corpus callosum body and splenium partial agenesis and a small interhemispheric arachnoid cyst, impaired rotation of the hippocampal cortex. Due to the possible association of intracranial vascular abnormalities in patient with Morning Glory Syndrome, the study was integrated with an MRA that detected bilateral supraclinoid ICA (intracranial internal carotid artery) and M1segment of MCA (middle cerebral artery) narrowing, with thin collateral lenticulostriate vessels, compatible with a diagnosis of Moyamoya syndrome. For a complete evaluation, also considering in the history of headache, we performed a DSC PWI study, that revealed a preserved cerebrovascular reserve capacity. During follow-up the patient developed also central hypothyroidism. Genetic evaluation was conducted through target gene sequencing of genes involved in hypopituitarism (*Gli2, Gli3, HESX1, LHX3, LHX4, OTX2, POU1F1, PROP1, SHH, SIX3, SOX3, TGIF, ZIC2*) and arrayCGH, resulted both negative. We are planning a whole exome sequencing.

We described a complex case of Morning Glory Syndrome including pituitary and corpus callosum anomalies, Moyamoya syndrome, with a rare new association with Persisting Embryonal Infundibular Recess, this information may be useful in neuroradiological evaluation for the correct interpretation of an apparently duplicated pituitary stalk on coronal images. Adequate follow-up is required in patients with midline anomalies and MCGA to look for vascular abnormalities and pituitary deficiencies.

Familial occurrence of Turner syndrome in two Tunisian families

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Background: Turner syndrome (TS) is a common genetic disorder with an incidence of 1 in 2500 live births due to chromosomal errors resulting in monosomy for the X chromosome with or without mosaicism. Familial TS has been rarely reported. We report two families having TS.

Methods: We report 6 patients with TS who had been referred to the Endocrinology department and Pediatric department at Hedi Chaker hospital, Sfax, Tunisia. We performed biochemical analysis, imaging and cytogenetic analyses.

Results: We report two families having TS. In the first, 4 sisters belonging to a consanguineous family were diagnosed at the age of 14, 17, 31 and 43 years, for TS because of the short stature dysmorphic syndrome and delayed puberty. The cytogenetic analyses performed showed different karyotypes 45XO, 45XO/46XX and two had 45X/46XX/47XXX and mother's karyotype analysis revealed no chromosomal abnormality. The second family included monozygotic twins having the same formula 45X/46XX. Their mother karyotype was not analysed. They were diagnosed at the age of 1 year because they suffered from dysmorphic syndrome. They had stature delay and both of them are now under growth hormone treatment.

Conclusions: In familial TS, mothers can carry a mosaic TS with an abnormal X and have normal fertility. But in our cohort mother's karyotype analysis revealed no chromosomal abnormality. Reported cases in the literature revealed chromosomal abnormality including mosaicism, presenting genetic defects which predisposed to chromosomal fragility and then chromosomal aneuploidy which can be hereditarily transmitted to the descendants. Thus, specific maternal karyotype should be taken into account in genetic counselling regarding potential risks for offspring. These cases suggest that a risk of recurrence is possible. And because of the clinical implications, TS families should be studied to exclude familial transmission.

P1-95**The role of physical activity on postural stability and fitness characteristics in pediatric patients with GH deficiency**

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Purpose: Patients with growth hormone deficiency (GHD) show low fitness levels before GH treatment is started. Muscular strength, flexibility and postural stability are related to health and quality of life. Since it is widely recognized that physical activity increases GH secretion and GH could ameliorate fitness, if a high adherence to treatment is documented (1), the purpose of this study is to investigate any difference on posturographic parameters and muscular features in physically active children with GHD, treated with GH with a high adherence to the treatment, and compared with sedentary pediatric patients.

Methods: 13 children (7 males, 6 females) with GHD were enrolled at the University Paediatric Unit of Palermo and assigned to either the physical activity group (PAG) or the sedentary group (SG), comprising 7 (age mean: 13,14±1,35 years; height: 142,14±11,39 cm; weight: 36,57±8,12 kg) and 6 (age mean: 12,67±2,5 years; height: 138,17±12,62 cm; weight: 34,67±15,77 kg) subjects, respectively. All participants were requested to perform a stabilometric test on a platform (freeMed® baropodometric platform, Sensor Medica®) and a fitness test battery including: a) hand grip test through a mechanical dynamometer (Kern Map model 80K1 - Kern®); b) counter movement jump; c) sit-up test; d) backsaver sit and reach test. Statistical analysis was performed using Statistica Software 12 (StatSoft®). The Student's t-test was adopted in order to determine any differences between groups with the *p*-value set at *p*<0,05.

Results: The stabilometric test showed a significant difference between groups on ellipse sway area (*p*<0,01) and sway path length (*p*<0,05) parameters. As concern fitness features, PAG showed higher values statistically significant (*p*<0,01) compared to SG on sit-up test. No significant differences (*p*>0,05) were found on hand grip test, counter movement jump and backsaver sit and reach test between groups.

Conclusions: Our preliminary findings suggest that in GHD children, treated with GH, physical activity ameliorates muscular strength levels and improves postural stability.

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P1-96**Assessment of subjective and objective compliance to growth hormone therapy of children with growth hormone deficiency**

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Introduction: The success of rhGH therapy is thought to be dependent on the patient's ability to maximally adhere to their treatment regimen.

Aim: To compare the reported (subjective) compliance as it was documented via a questionnaire fulfilled by the parents and/or patients, with actual (objective) compliance as recorded by a delivery device, to rhGH therapy.

Material and Methods: The study population consisted of 84 GH deficient children and adolescents (70 boys) with no underlying disease treated with GH. The reported compliance was recorded through a questionnaire and the actual compliance was retrieved through the special software from the dispenser (EasyPod). The Intraclass Correlation Coefficient (ICC) was used to compare the reported monthly compliance to treatment using the SPSS 25 statistical package.

Results: The mean age of the sample was 12.6 ± 1.9 years and the mean duration of treatment was 1.9 ± 1.5 years. The level of compliance was high (loss of <2 injections per month) in the majority (87.5%). of the patients. There was a moderate degree of agreement between the two measurements, with $ICC = 0.531$ (95% CI 0.313-0.692) ($F(64.64) = 3.588$, $p = 0.0005$). The level of the actual monthly compliance in treatment was positively correlated with the child's age ($rs(64) = 0.272$, $p = 0.030$).

Conclusions: Previous data suggest positive correlations between adherence and growth outcome, supporting the clinical relevance of adherence monitoring. Assessment of the degree of compliance with growth hormone treatment is a key to the proper adjustment of the dose and assessment of the efficacy of the treatment. Systematic recording via questionnaires is helpful however the objective recording through the delivery device reveals the real dimensions of the issue.

Pituitary, Neuroendocrinology and Puberty

P1-97

Familial Neurohypophyseal Diabetes Insipidus and 2 Novel Vasopressin Gene Mutations in 13 Italian Kindreds

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Background: Autosomal dominant neurohypophyseal diabetes insipidus (adNDI) is characterized by arginine vasopressin (AVP) deficiency resulting from mutations in the AVP-NPII gene

Patients and Methods: We analyzed AVP-NPII gene in 13 kindreds with familial NDI

Aim: To describe the clinical and molecular features of Italian kindreds with adNDI

Results: Twenty-two patients had a pathogenic AVP-NPII gene mutation. Two novel c.173 G>C (p.Cys58Ser), c.215 C>A (p.Ala72Glu) missense mutations and additional 8 different mutations previously described were identified; nine were missense and 1 non sense mutation. 8 out of 10 mutations occurred in the region encoding for the NPII moiety; 2 mutations were detected in exon 1. No mutations were found in exon 3. Median age of onset was 32.5 months with a variability within the same mutation (3 to 360 months). No clear genotype-phenotype correlation has been observed, except for the c.55 G>A (p.Ala19Thr) mutation, which led to a later onset of disease (median age 120 months). Brain magnetic resonance imaging (MRI) revealed absence of posterior pituitary hyperintensity in 8 out of 15 subjects, hypointense signal in 4 and normal signal in 2. Follow-up MRI showed the disappearance of the posterior pituitary hyperintensity after 6 years in one case.

Conclusion: adNDI is a progressive disease with a variable age of onset. Molecular diagnosis and counseling should be provided to avoid unnecessary investigations and to ensure an appropriate treatment.

P1-98

Final height in oncological growth hormone deficient (GHD) children after growth hormone (GH) therapy

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Background: Growth hormone deficiency (GHD) is the commonest hypothalamic-pituitary (HP) disorder in cancer survivors. The only few studies in literature addressing GH efficacy in a large cohort of patients concluded that, though improving height outcome, GH therapy may not entirely restore final height (FH) potential according to mid-parental height (MPH). Thus, in order to optimize outcome, more information on factors influencing growth response in these children is needed.

Design and Methods: This was a retrospective study on final height in 87 children (M=54) who received GH (first 2 years mean dose 0.026 ± 0.006 mg/kg/day) for GHD secondary to tumours treated with cranial radiotherapy (Rx) (Group A, n=40), craniospinal Rx (n=23) and total body Rx (n=16) (Group B, n=39) or tumours involving HP area who didn't receive Rx (Group C, n=8). 19/87 patients with central precocious/early puberty also received GnRH analogs (GnRHa). In 45/87 patients MPH was retrieved (20 Group A; 25 Group B). We evaluated GH efficacy as 1st and 2nd year response, FH and height loss (HL) at FH (Δ FH-MPH SDS) and the contribution of several independent variables to FH and HL.

Results: Patients showed an overall good response during the 1st and 2nd year of therapy (HT gain 0.38 ± 0.35 SDS and 0.18 ± 0.30 SDS, $P<0.0001$, respectively), with a mean FH in the normal range (-0.85 ± 1.34 SDS) though not significantly different from HT SDS at GH start (-0.88 ± 1.17 SDS). 15/87 had a FH<-2SDS and this was more frequently encountered in Group B (11/15, $P=0.006$). 67% (30/45) failed to reach their MPH, with a HL at FH of -0.67 ± 1.41 SDS ($P=0.0027$). This was more evident in Group B, where only 2 children achieved their MPH ($P<0.0001$). However, HL at FH improved or remained stable compared to baseline in 26/45 patients (58%). At stepwise regression, the most important determinants of FH were HT at baseline and lag time ($B=0.91\pm 0.18$, $P<0.0001$ and $B=-0.46\pm 0.17$, $P=0.012$, respectively). There was no significant difference in FH among patients treated for CPP/early puberty and the remaining patients (-0.84 ± 1.32 SDS vs -0.86 ± 1.35 SDS).

Conclusion: Compared to published data, our study showed one of the best results considering both short and long-term outcomes of GH treatment. GH and GnRHa therapy, when indicated, though failed to induce catch-up growth, prevented further height loss, leading to a FH within the normal range but still below MPH, especially in children who received craniospinal or total body Rx. Our study confirmed the importance of early GHD diagnosis and prompt GH replacement.

P1-99

Eating Behavior and Oxytocin in Childhood-onset Craniopharyngioma Patients: An Exploratory Study

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Background: Childhood-onset craniopharyngioma patients (CP) often suffer from tumor or treatment-related hypothalamic lesions (HL). These lesions may alter production of oxytocin, which plays a major role in the regulation of eating behavior and body composition.

Objective: In CP with different degrees HL, we investigated associations between HL, eating behavior/eating attitudes, and oxytocin saliva concentrations (OSC).

Methods: In a cross-sectional case-control study on 34 CP and 73 healthy controls, OSC were measured before, and 60 min after breakfast by immunoassay. Eating behavior, attitudes and habits were assessed by standardized questionnaires.

Results: CP with anterior+posterior HL presented with more adverse eating behaviors/symptoms of eating disorders than CP without HL, CP with anterior HL, and controls. Eating behavior in CP with anterior HL was similar to controls, except for their tendency towards high dietary restraints. Decreases in postprandial compared to fasting OSC were associated with adverse eating behavior in CP and controls and with higher BMI in CP.

Conclusions: CP with anterior HL and CP with anterior+posterior HL present with distinct patterns of eating behavior. Reduced postprandial compared to fasting OSC is associated with weight problems in CP and with adverse eating behavior and symptoms of eating disorders in both CP and controls.

P1-100

RNPC3 mutations associate prolactin deficiency and ovarian insufficiency, expanding the phenotype beyond isolated growth hormone deficiency type V (MIM#618860)

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Background: The first three children reported to have biallelic mutations in RNPC3 presented with growth hormone (GH) deficiency and pituitary hypoplasia (MIM#618860). RNPC3 codes for a minor spliceosome protein required for U11/U12 small nuclear ribonucleoprotein formation and splicing of U12-type introns. The underlying mechanism causing GH deficiency in these patients is not fully understood. Moreover, whether the association of further hormonal deficiencies occurs throughout lifespan is unknown.

Objective: To analyze the evolving hormonal phenotype throughout childhood and adolescence in the first three patients identified with RNPC3 mutations.

Results: Clinical follow-up and rhGH replacement of the three sisters started at age 15.5 (patient-1), 8.1 (patient-2) and 6.0 (patient-3) years (y), respectively. Patient-1 showed slightly decreased serum prolactin levels at diagnosis (0.78 ng/ml [NV: 1.6-25]), with normal levels in patient-2 (2.12 ng/ml) and 3 (1.83 ng/ml). In contrast, when these patients reached ages of 23, 15.7 and 13.7 y, respectively, in all three serum prolactin was undetectable in three separate baseline determinations and after TRH stimulation. Patient-1 was Tanner stage I at diagnosis, with baseline FSH: 30.3 (NV: 2-22) and LH: 6.7 mU/ml (NV: 0.6-56) peaking after LHRH stimulation at 40.1 and 35.5 mU/ml, respectively, and concomitant low serum estradiol levels [7.4 pg/ml (10-400)]. Three months after rhGH treatment was started, Tanner stage II spontaneously developed, progressing to Tanner stage IV after 12 months and presenting a spontaneous 4-day menarche after 16 months on therapy. No further menstrual cycles occurred, with low serum estradiol levels persisting and normal to high FSH and LH levels both at baseline and after LHRH stimulation, thus requiring hormone replacement. Patient-2 spontaneously started puberty (Tanner stage II) at 11.6 y, progressing to Tanner stage IV at age 13 y, but remaining without menarche up to her last evaluation (age 15.7 y), with baseline estradiol 9.8 pg/ml, FSH 44.2 and

LH 12 mU/ml, peaking after LHRH stimulation to 63.1 and 49.5 mU/ml, respectively. Patient-3 started spontaneous pubertal development at age 13.0 y, progressing to Tanner stage II in the following 6 months (last visit). Normal size ovaries but with sparse or absent follicles were found in patients 1 and 2 by ultrasonography.

The tyrotrophic and corticotrophic axes have shown no impairment during the follow-up to date.

Conclusion: Patients with *RNPC3* mutations, initially presenting as isolated GH deficiency, can develop additional pituitary (prolactin) or peripheral (estradiol) hormone deficiencies throughout lifespan.

P1-101

Identification of novel mutations in FGFR1 and functional characteristics in patients with isolated gonadotropin-releasing hormone deficiency

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Background: Isolated gonadotropin-releasing hormone (GnRH) deficiency (IGD) is caused by a deficiency in GnRH production, secretion or action and a highly heterogeneous disorder with wide phenotypic spectrum including Kallmann syndrome (KS) with anosmia and normosmic idiopathic hypogonadotropic hypogonadism (nIHH). More than 30 different causative genes have been identified in several studies. *FGFR1* mutations have been identified in about 3–10% of patients with Kallmann syndrome or nIHH. This study was performed to investigate the clinical phenotypes and to assess functional characteristics of *FGFR1* mutations in patients with IGD.

Methods: Mutation analysis of *FGFR1* was performed in 49 subjects with IGD using targeted gene panel for 69 genes (n = 34) or whole exome sequencing (n = 15). The impact of the identified mutations on *FGFR1* function was assessed using *in vitro* studies.

Results: Six novel heterozygous mutations in *FGFR1* were identified in 6 unrelated patients (12.2%): p.Y210*, p.Y339H, p.S681I, c.1855-1G>A, c.1663+2T>G, and c.551dup (p.N185Kfs*16). They exhibited a wide clinical spectrum with altered pubertal development, ranging from KS (n = 1), nIHH (n = 4), and a prepubertal male with anosmia. Four adult males manifested delayed puberty or micropenis, while a female subject presented with primary amenorrhea at age 19 years. A 7-year-old male presented with anosmia and absence of olfactory bulbs. Patients with p.Y339H and c.1855-1G>A revealed osteoporosis and finger syndactyly, respectively. Wild-type (WT) and *FGFR1* mutants (p.Y339H and p.N185Kfs*16) were transiently transfected into L6 myoblasts with an *FGFR1*-responsive osteocalcin promoter luciferase construct. FGF8 treatment of WT *FGFR1* induced an increase in LUC

reporter gene expression. Total RNA was extracted from peripheral blood using a PAXgene blood RNA kit and RT-PCR was performed in the patients with a c.1663+2T>G mutation, resulting a skipping of exon 11.

Conclusions: This study identified six novel mutations in *FGFR1* mutations in 12.2% of subjects with KS and nIHH. Inactivating mutations in *FGFR1* occur at a high frequency in IGD patients. Probands carrying an *FGFR1* mutation displayed a wide phenotypic spectrum ranging from KS to anosmia. A prepubertal male with anosmia should be followed up to assess pubertal development.

P1-102

Clinical Presentation, Management, and the Outcomes of Pituitary Adenomas in children

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Introduction: Pituitary adenoma (PA) in childhood is a rare disease, accounting for 3 % of all intracranial paediatric neoplasm, and between 3 to 6% of all PA. There are only few large studies describing paediatric pituitary adenoma and even fewer studies with long-term outcome.

Methods: In this retrospective study, clinical, biochemical and radiological parameters and outcome of paediatric patients (<16 years of age at diagnosis) with PA diagnosed between 2000 and 2019 were analysed.

Results: 23 patients with PA were identified with median follow up of 3.27 years (range 0.6 to 8.43): 12 prolactinomas (52%, median age: 15 years, range 13–16 years; 12 females), 6 non-functioning pituitary adenomas (NFPA) (26%, median age: 16 years, range 12–16 years; 2 females) and 5 adrenocorticotrophic hormone (ACTH) adenomas (22%, median age: 13.5 years, range 4–15 years; 2 females). Prolactinomas consisted of nine macro (diameter 11mm–35mm) and three microadenomas (diameter 4–10 mm). Patients with prolactinoma presented with menstrual irregularities (67%), headache (50%), galactorrhoea (41%), and weight gain (41%). Cabergoline was effective in 9 patients, 3 required surgical intervention and 1 patient had recurrence after surgery and required radiotherapy. ACTH adenomas presented with weight gain (median BMI: 2.96 SDS; range: 2.12 to 5.47 SDS), short stature and headache. Operative tumour resection was performed in ACTH adenomas; 2 had recurrence and required radiotherapy while 1 patient required bilateral adrenalectomy (post-surgery and radiotherapy). All patients with ACTH adenomas developed multiple pituitary hormone deficiency (MPHD) post-surgery. Weight gain, visual field defects and headache were the presenting features in NFPA. Four required surgical intervention; two had recurrence post-surgery and required radiotherapy. On latest follow-up; 13 (56%) patients were obese (median BMI 3.09 SDS; range: 2.05 to 3.79 SDS). Five patients with aggressive

disease required surgery and radiotherapy and suffered from post treatment weight gain (median BMI: 2.12 to 2.25 SDS).

Conclusion: Prolactinomas are the most common PA in children. Adolescents with headaches and menstrual irregularities should be investigated for prolactinoma. Cabergoline is effective in patients with prolactinoma in alleviating clinical symptoms, reducing prolactin concentrations and inducing tumour shrinkage. ACTH adenomas lead to aggressive disease and complete tumour resection could ameliorate clinical signs but can be complicated by recurrence. Surgery should be considered as first-line treatment in ACTH adenomas and in NFPA with visual impairment. Obesity is an important sequel and active identification and treatment is necessary.

P1-103

A case of panhypopituitarism with SOX3 gene deletion

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Introduction: It is known that microduplications including the SOX3 gene and intragenic duplications leading to loss of function in the gene cause panhypopituitarism, which can be accompanied by intellectual failure. Here, we report the first known case of panhypopituitarism, a deletion of the X chromosome, including the SOX3 gene in the q27.1q27.3 region.

Case: A 15-years and two months old male patient was referred to our clinic because of short stature, delay in puberty, and a reversal of the bone age. He had a history of mild mental retardation. He were born 3000 gr in term. There was no consanguinity between the parents. Physical examination revealed weight: 45,7 kg (<3p), height: 141,8 cm (<3p), height SDS -4.14, bone age 11y, 4-5. metacarpal shortening, low-narrow shoulder, scrotum hypoplasia, testicular volume was 6 / 6 ml. Karyotype analysis was 46, XY. IGF1: 60.4 mg / dl (<-3SD), IGFBP3: 3297 (-2, -3SD), L-Dopa test peak growth hormone 0.66 mg / dl, clonidine test peak growth hormone 0.98 mg / dl. growth hormone treatment was started due to hormone deficiency. In the LHRH test, peak FSH: 3.55 U / L, peak LH: 3.9 U / L was detected. In the CGH analysis of the patient, there was a 3,961 kb deletion in the q27.1q27.3 region of the X chromosome containing the SOX3 gene.

Discussion: It is known that duplications containing SOX3 gene in the q27 band region of X chromosome cause panhypopituitarism, short stature and learning difficulties. In addition, intragenic duplications that lead to loss of function in the SOX3 gene cause panhypopituitarism. In other words, both high dosage and loss of function in the SOX3 gene are responsible for panhypopituitarism. In our patient, the deletion which caused null variance in SOX3 gene was thought to be responsible for panhypopituitarism, behavioral problems and speech deceleration. Our case is important in terms of being the first patient with SOX3 nulldelelness and panhypopituitarism.

P1-104

Interesting Genotype-Phenotype Differences in Siblings with Familial Hypopituitarism and Pituitary Hypoplasia

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Context: The majority of congenital isolated growth hormone deficiency (IGHD) cases are idiopathic. Recent research has shed light on the genetic aetiologies of congenital hypopituitarism. HESX1 and GLI2 are two transcription factors, amongst a cascade of other transcription factors and signalling molecules, involved in the development of the pituitary gland. Mutations in both genes have been shown to cause congenital hypopituitarism with varying phenotypes.

Case: We report varying clinical presentations of IGHD in two siblings from a non-consanguineous family. The index case presented at 14 months with failure to thrive (FTT), underdeveloped genitalia, post axial polydactyly of his left foot, previous history of developmental dysplasia of hip and neonatal hypoglycaemia. He had significant mid-facial hypoplasia, prominent forehead and ears. He also has mild developmental delay and hearing impairment. The younger brother presented at 8 months with FTT and has milder phenotypic features of mid facial hypoplasia.

Both siblings have low IgF-1, IGHD, with MRI findings of severe pituitary hypoplasia and Chiari 1 malformation. The older sibling's genetic analysis revealed a pathogenic variant in paternally derived HESX1: c.475C>T, p. (Arg159Trp) and maternally derived GLI2 c.2671dupG, P. (Ala891Gly*140). The younger brother was found to have a maternally derived heterozygous GLI2 variant.

Both siblings have done exceedingly well on growth hormone therapy and have not developed multiple pituitary hormone deficiency (MPHD).

Discussion: We present an interesting case of a double gene hit; with pathogenic mutations in HESX1 and GLI2, and explore the possibility of pituitary gene interactions in the phenotypic differences.

HESX1 mutations are typically associated with MPHD and septo-optic dysplasia (SOD). SOD is highly heterogeneous condition with multi-factorial aetiology, and HESX1 causes SOD by oligogenic interaction.

GLI2 mutations have been associated with holoprosencephaly (HPE) or HPE-like features with pituitary abnormalities and polydactyly. In the last decade, there is evidence gathering which suggests that pathogenic variants, especially loss of function (severe) variants, lead to mainly anterior pituitary hypoplasia, and less commonly posterior pituitary ectopy and post axial polydactyly. Two-thirds of individuals with loss of function variants in GLI2 (nonsense, frameshift canonical splice site variants) have both pituitary deficiency and polydactyly, whereas in those with milder missense variants, these features occur more rarely in combination. There is often wide phenotypic variability, even in the same family. Even the severe loss of function variants are often inherited from an unaffected normal parent suggesting variable penetrance and likely effects of other genes or environmental factors.

P1-105**Familial Central Precocious Puberty Caused by a Novel MKRN3 Mutation**

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Background: Mutations in the imprinted gene *MKRN3* have been associated with inherited central precocious puberty (CPP). *MKRN3* is a maternal imprinted gene and the disease is exclusively paternally transmitted in an autosomal dominant manner. Although the mechanism is unclear, it has been suggested that *MKRN3* inhibits hypothalamic GnRH release, leading to a loss-of-function mutation and CPP. To date, more than 20 *MKRN3* mutations have been reported.

Methods: Six patients (3M, 3F) with CPP from highly consanguineous families were enrolled. *MKRN3* was sequenced for the proband and the identified mutation was screened in 13 family members.

Results: CPP was diagnosed based on clinical and hormonal findings in 6 children belonging to 2 related families. Five were treated with GnRH analog. The age of pubertal onset in the girls ranged from 5 to 6.5 years and in the boys, from 7 to 8 years. The familial occurrence of CPP raised the diagnosis of *MKRN3* mutation; *MKRN3* sequencing revealed a novel heterozygous loss-of-function missense mutation, c.1033C>T; p.Arg345Cys. This mutation is located within a zinc finger motif predicted to be involved in RNA binding, essential for protein function. Nine family members were heterozygous for the identified mutation, including 2 parents of family 1 and the father of family 2. Two children of family 1 were homozygous for the same mutation inherited both maternally and paternally. Two non-affected members were negative.

Conclusions: We report a novel *MKRN3* mutation in highly consanguineous families with multiple cases of CPP. This is the first report of homozygosity for an *MKRN3* mutation, indicating that the phenotype in these cases does not differ from the phenotype of heterozygous patients. *MKRN3* sequencing is recommended in familial CPP.

P1-106**Management and treatment outcome of craniopharyngiomas in young children before 4 years of age in Italy: multicentre collection of 16 cases**

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Introduction: Craniopharyngiomas (CP) are rare pediatric intracranial tumors (1.2-4%) with a peak of incidence between 5-14 years. We retrospectively reviewed data of 16 cases (M/F 4/12) diagnosed before 4 years of age (median follow up 7.2 years) from a cohort of 117 patients (pts) (M/F 56/41) diagnosed after 01/01/2000, followed-up in 14 Italian centres of pediatric endocrinology belonging to the Italian Society for Pediatric Endocrinology and Diabetology.

Results: The pts were treated in 8 different centers across Italy. Median age at diagnosis was 2.7 years (yrs) (range 0.1-3.7) with a delay of 6 months (0-2.3 yrs) from the symptoms onset: visual impairment (5 pts), headache (6 pts), vomiting (4 pts), polyuria/polydipsia (2 pts), ataxia (1pt), fatigue (1pt). One pt was diagnosed prenatally. Neuroimaging showed 2 solid, 5 cystic and 9 mixed tumors, localized intrasellar (3 pts) and suprasellar (13 pts), with 3rd ventricle involvement in 8 pts. Median tumor size was 34.5 mm (range 30-70). The surgery approach was transsphenoidal (TS) in 5 pts (31%), craniotomy (CT) in 11 pts (69%). Radical tumor removal was obtained in 10/16 pts (62%). Histology confirmed adamantinous CP in 15/16 cases and papillary CP in one case. 12/16 pts early after surgery started the substitutive treatment with l-thyroxin, hydrocortisone and DDAVP for multiple pituitary hormone deficiencies.

11/16 cases started hGH treatment (median dose 0.07-0.2 mg/kg/wk) after 1.28 (0.5-2.6) years after diagnosis of CP for GH deficiency and growth impairment.

Recurrences occurred in 11/16 pts (69%), 1 in 4 pts, 2 in 6, 3 in 1. The first relapse occurred 6 months (range 0.4-4 yrs) after surgery, in 5/11 pts despite radical tumor removal. Recurrences were treated with surgical reintervention, associated with radiotherapy in 5 cases (1 γ-knife, 2 proton, 2 conventional). In the 5 patients who underwent TS radical surgery no CP relapses arose until last

control. 3 /11 pts relapsed during the first 2 years of GH treatment. 4/16 (3 CT/1 TS) pts showed overweight at last control with BMI SDS 1.8-2.6, 3/4 with hypothalamic syndrome (HS).

Conclusion. CP in our children showed an aggressive behavior, with severe symptoms at diagnosis, relapsed in 69% of cases even in those with radical removal. In all cases at least 3 pituitary hormone deficiency arose after treatment, hGH seems not to increase the incidence of recurrences. HS is a frequent complication irrespective of type of surgery.

P1-107

Secular trend of age at menarche and stature in Tuscan girls: a retrospective study in the birth cohort 1995-2003

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Introduction: Developed countries have shown, among the 20th century, a time trend towards a younger age at menarche. Tanner described an anticipation of 3 months every decade. In the last two decades of twenty century we have observed an apparent stabilization of menarche age in most of Western countries.

Objective: analyze average age of menarche in Tuscany girls and compare our results with those in literature to observe the persistence or not of stabilization of this parameter; analyze average age of breast button appearance in the same population and correlate menarche age with height and BMI, in order to look for relationships between these.

Patients & Methods: we've extrapolated data from databases of 11 Family Pediatric Studies in the provinces of Pistoia and Florence. We've collected the parameters of 1121 girls born between 1995 and 2003, with menarche already happened at the time of the study. The data we evaluated are: menarche age; age of B2 appearance; height and weight measured at the time of menarche and of the last visit carried out by the pediatrician. Finally, we compared the data with the previous data of Rigon et al. (2010) and Bona et al. (2002) in the Italian population.

Results: the average age of menarche is $12,07 \pm 3,29$ years ($p<0.0001$ vs. the data of Rigon et al) disclosing an anticipation of the menarche age; the mean age of breast button appearance is $10,18 \pm 3,39$ years ($p<0.05$ in comparison with those of Bona et al.) showing an anticipation of B2; the mean menarche age in girls with BMI between 3° and 95° percentile corresponds to $12,05 \pm 3,19$ years, the one of underweight children (BMI <3° percentile) is $12,74 \pm 3,51$ years, while the one of obese girls (BMI >95° percentile) is $11,46 \pm 2,85$ years ($p<0.005$). We observed a statistically significant relationship between SDS BMI and menarche age ($p<0.0001$). The average adult height calculated in the cohort which has been spent at least 2 years between menarche and last visit corresponds to $161,47 \pm 7,81$ cm.

Conclusions: our results suggest a restart of the anticipatory trend of menarche age and of appearance of breast in Italian Girls. We also observe a significant relationship between BMI and the age of first period and between the age of menarche and final height. The definitive average height seems to be conform to the one of the Italian female population (162 cm).

P1-108

Hyperprolactinemia in children with juvenile idiopathic arthritis

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Background: Multiple causes of hyperprolactinemia can be identified in some patients with rheumatic diseases. Prolactin maintains cartilage maintenance, osteogenesis, growth, proliferation and apoptosis as well as the release of proinflammatory mediators by immune cells – events that can both induce and prevent rheumatic diseases. The aim of this study is to analyze the serum prolactin level in patients with juvenile idiopathic arthritis (JIA), and their association with demographic and disease indices.

Methods and Materials: The study included 100 children with juvenile idiopathic arthritis. We assessed basal serum prolactin levels in correlation with the JIA duration and activity indices. The JIA diagnosis was established based on the ILAR / ACR criteria.

Results and Discussion: The demographic indexes of subjects in the study revealed: mean age 9.38 years, mean age at onset - 6.4 years, mean disease duration - 5.35 years, gender distribution 1: 1.47. The oligoarticular form was found to be in 43%, the seronegative polyarticular form in 27.6% and the systemic form 24.8%. The JADAS-71 score averaged 23.35 points. Paraclinical findings revealed hyperprolactinemia in 6 of 50 patients (12% of cases; girls: boys = 4: 2). Clinical manifestations of specific conditions with hyperprolactinemia (galactorrhea, disturbance of visual field, pituitary tumor syndrome) have not been identified. In 2 out of 6 patients, periodic headache was noted. Serum prolactin abnormalities correlate with disease activity (JADAS score > 25 points in all cases with hyperprolactinemia) and low onset age (1.5-2.5 years).

According to literature data, prolactin along with estrogen is pro-inflammatory hormones, and high levels in women explain the high proportion of women: men. The correlation of hyperprolactinemia with the indices of the activity of many rheumatologic conditions are still contradictory. Both hypo- and hyperprolactinemia induce immunocompromised conditions. TNF α and IL-6 have the potential to stimulate prolactin secretion, which is another cause of hyperprolactinemia in patients with rheumatic diseases.

Conclusions: In conclusion, elevated serum levels of prolactin in cases of idiopathic juvenile arthritis may possibly suggest its role in autoimmune response. Identification of endocrine comorbidities in juvenile idiopathic arthritis, aims to prevent and limit the impact of disease on child development.

P1-109**A NCOA5 gene variant in a pedigree with maternally inherited precocious puberty**

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Background: The major genetic causes of CPP are the paternally inherited Makorin RING-finger protein 3 (MKRN3) and Delta-like homolog 1 (DLK1) deficiencies. Exceedingly rare patients with CPP carry variants in kisspeptin system. The CPP genes are also associated with the age at menarche in the population as demonstrated by genome-wide association studies (GWAS). Nuclear Receptor Coactivator 5 (NCOA5) is a coregulator for the alpha and beta estrogen receptors and is associated with the age at menarche by GWAS.

Objectives: To identify novel genetic causes of CPP.

Population and Methods: Whole genome sequencing (WGS) of 14 family trios and one additional proband affected with familial CPP, demonstrating maternal (10 pedigrees) or paternal / recessive inheritance pattern (5 pedigrees), was performed. In additional 38 probands (13 girls with maternally inherited CPP, 5 sporadic boys, 20 sporadic girls with CPP onset before 7 years) whole exome sequencing (WES) was performed. Coding regions of 398 genes reported to be associated with age at menarche by GWAS were analysed for rare variants (MAF<0.2%) by targeted approach. Genetic variants with coverage >10x were retained and analysed with Variant Studio 3.0 software. Identified candidate variants and their family segregation were verified by Sanger sequencing. Coding variants in the MKRN3 gene were pre-screened and excluded by Sanger sequencing in all probands without obvious dominant maternal inheritance.

Results: In a pedigree with maternal inheritance a rare missense variant p.R70W (gnomAD allele frequency 1.59e-5) *in silico* predicted to be pathogenic (CADD score 26.6) in NCOA5 gene was identified by WGS. The variant segregated with CPP or early puberty in the mother (menarche at 10 years), and two sisters. The proband carrier had telarche at the age of 6 years with markedly advanced bone age (+3.5 SD), tall stature (+3.3 SD) and increased basal and GnRH-stimulated luteinizing hormone (LH). Her older sister had telarche, pubertal LH levels, growth acceleration and bone age advancement (+1.65 SD) at the age of 8 years. No other NCOA5 coding variants and no DLK1 variants were identified in the rest of the cohort.

Conclusions: A rare variant of unknown significance in a gene implicated in the regulation of estrogen receptors, NCOA5, was identified in a pedigree with maternally inherited CPP. The implication of identified variant on NCOA5 function and CPP phenotype remains to be determined. Variants in DLK1 gene were not a common cause of CPP in our cohort.

P1-110**References for testicular volume measured by ultrasound and for pubic hair in 6-16 year-old Norwegian boys**

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Objective: Recent studies have suggested earlier onset of pubertal development in boys. As assessment with orchidometer tends to overestimate true testicular volume (TV), and measurements based on ultrasound (US) have been proposed as a more reliable method, we present US based references in 6-16 year-old Norwegian boys. Our results are compared with data from Europe and the United States (U.S.) in order to establish evidence for an ongoing secular trend in male pubertal timing.

Methods: TV was measured by ultrasound in a cross-sectional study of 514 healthy boys (mean age 11.0 year, range 6.1-16.4) and reference curves were constructed using the LMS method. Tanner pubic hair (PH) staging was clinically assessed in 453 boys (mean age: 10.9 years, range: 6.1 to 16.3). Pubertal development was determined in terms of selected TV cut points or the PH stages and related to age using simple probit regression models.

Results: US testicular volume of 2.7 ml, corresponding to orchidometer definition of puberty onset volume of 4 ml, was on average reached at mean (standard deviation: SD) 11.7 (1.1) years with the 3rd and 97th percentile at 9.7 and 13.7 years, respectively. TV by age was positively skewed. Mean age (SD) for reaching Tanner PH stage 2 was 11.8 (1.2) years with 3rd and 97th percentile at 9.5 and 14.1 years, respectively. Our findings were highly comparable with previous published data from Europe and the U.S.

Conclusion: New references for TV measured by US and equivalent orchidometer volumes were constructed together with pubic hair references. US provides a continuous measure allowing

for accurate SD score calculations. No secular trend in pubertal development in boys was observed indicating that the definition of normal pubertal onset in boys between 9 to 14 years remains statistically valid.

P1-111**PROKR2 in girls with idiopathic central precocious puberty**

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Introduction: PROKR2 is a 384-amino acid G-protein-coupled receptors (GPCR) that regulates GnRH secretion in the hypothalamus. PROKR2 mutations have been described as cause of a certain percentage of hypogonadotropic hypogonadism and Kallmann syndrome.

In 2017 a heterozygous frameshift gain of function mutation of PROKR2 was identified in a 3.5-year-old girl with central precocious puberty (CPP).

The aim of our study was to perform a mutation screening of such gene in girls with “early” onset CPP (first signs of puberty occurred \leq 6 years of age).

Materials and Methods: We enrolled 25 girls with idiopathic CPP with pubertal basal LH level or pubertal LH response to GnRH testing (mean age at first observation 5.5 years, range 2-7; mean age at first occurrence of thelarche 5 years old, range 1-6).

Results: No rare variants were identified. Five polymorphisms were found (rs6076809, rs8116897, rs3746684, rs3746682, rs3746683). All except one (i.e. rs3746682) had a minor allele frequency (MAF) similar to that reported in literature. rs3746682 presented a MAF higher than described in The Exome Aggregation Consortium (ExAC) (0.84 in our population vs 0.25 from ExAC).

Conclusions: Our data suggest that mutations in PROKR2 gene are not a frequent cause of central precocious puberty in girls, even in subjects with a very early onset CPP. As for other G-protein-coupled receptors (i.e. GPR54), gain of function mutations affecting these kind of hypothalamic regulating factors are a very rare cause of CPP in girls. The significance of the different MAF of rs3746682 polymorphism has to be investigated in larger samples of patients and controls.

P1-112**The Relationship between the Olfactory Bulb and Precocious Puberty: From Nose to Pituitary**

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Background/Objective: The olfactory bulb (OB) and pubertal development have a close relationship as they share a common ontogenetic origin. The aim of this study is to analyze the potential relationship between the precocious puberty in girls as a sign of early pubertal timing and their OB volume as an indicator of its functional activity.

Design: In the study group (n=125), OB volume, pituitary height, body mass index (BMI), body surface (S) variables were retrospectively investigated in 49 girls included in the precocious puberty (PP) group and 76 healthy girls constituting the control group. Volumetric and length measurements were performed on MRI scan by using manual segmentation of slices.

Results: Mean OB volume ($73.41 \pm 17.21 \text{ mm}^3$) and pituitary height ($4.96 \pm 1.01 \text{ mm}$) were significantly higher in the PP group ($p=0.001$, $p=0.001$, respectively). The mean volume difference between the right and left bulbs (1.52 ± 1.87) was higher in the PP group ($p=0.03$). Body surface ($1.05 \pm 0.16 \text{ m}^2$) was larger in the PP group ($p=0.09$). There was a high correlation between OB volume and pituitary height ($r_{125}=0.716$). There was a moderate correlation between body surface and OB volume ($r_{125}=0.654$), and a weak correlation between the former (S) and pituitary height ($r_{125}=0.452$).

Conclusion: This study has shown a marked increase in OB volume and an increase in pituitary height in PP and a strong correlation between these two variables which indicates that OB, i.e. the pathway from the nose to the brain, still has an effective functioning role in the underlying mechanisms of pubertal timing.

P1-113**Delayed puberty in a 16-year-old male associated with gamma aminobutyric acid capsule supplements**

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Background: Delayed puberty is defined as the absence of physical signs of puberty 2 to 2.5 standard deviations greater than the mean and affects 2% of the adolescent population. We present a male patient aged 16, presenting with delayed puberty. On direct questioning the patient revealed he had been taking regular Gamma-Aminobutyric Acid (GABA). These supplements appeared to suppress the hypothalamic-pituitary-gonadal (HPG) axis.

Case Presentation: A 16-year-old male patient presented to primary care with concerns about a lack of pubertal development. No significant past medical history was noted. No family history of delayed puberty was elicited. The patient revealed he had been taking over the counter GABA capsules to help alleviate stress and improve sleep.

On examination the patient had no secondary sexual characteristics. His pubic hair was sparse, testicular volume was 5ml and the external genitalia were consistent with Tanner stage 2. His height was within two centile spaces of the mid-parental centile and BMI appropriate for age.

Initial investigations showed; Serum testosterone (7.7 nmol/L [10-28 nmol/L]), Luteinising hormone (LH) 2.0 IU/L [2-9 IU/L] and Follicle Stimulating Hormone (FSH) 2.4 IU/L [1-12 IU/L]. A subsequent Gonadotrophin Releasing Hormone (GnRH) test confirmed a suppressed HPG axis [basal LH 1.9 IU/L, with stimulated peak of 2.8 IU/L, basal FSH 1.1 IU/L, with stimulated peak of 1.6 IU/L].

Following cessation of the GABA capsules there was immediate recovery of the HPG axis. A repeat GnRH test, performed two weeks following cessation of the medication showed an LH dominant response [Basal LH 5.6 IU/L, with a stimulated peak of 16.1, basal FSH 5.3, with stimulated peak of 7.5].

Following the discontinuation of GABA capsules, the patient was monitored over a period of six months. Consonant puberty has progressed and the patient is now Tanner stage V. No further concerns were noted. The patient was subsequently discharged from clinic.

Conclusions: In recent years there has been a significant rise in the sale of oral GABA capsules as food supplements, manufacturers report that the supplements can alleviate stress, reduce anxiety and help improve sleep disorders. Despite these claims there are few good quality studies which have clearly demonstrated that GABA supplementation can improve such symptoms. To our knowledge this is the first reported case of GABA supplements causing suppression of the HPG axis and subsequent pubertal delay.

P1-114

Obesity in boys is not associated with delayed pubertal onset

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Context: Pubertal timing in boys is associated with body mass index (BMI). Studies consistently report an inverse correlation of BMI and pubertal timing within the normal BMI range. However, observations in obese boys are conflicting with different studies reporting either early or delayed pubertal onset in obese boys.

Objectives: We aimed to assess the association of clinically assessed initial milestones of male puberty, i.e. gonadarche, testicular enlargement and pubarche, with age-specific BMI (zBMI) in obese boys.

Participants & Methods: Cases: 254 obese boys (zBMI >2SD, median age at baseline 11.2 (range: 4.2 to 17.4) were recruited as part of an outpatient childhood obesity intervention program at Nordsjællands Hospital, Denmark between 2009 and 2017. Controls: 127 overweight (zBMI >1SD and ≤2SD) healthy boys participating in The Copenhagen Puberty Study (entire cohort: n = 731, zBMI range: -2.5 to 2.5 SD, mean age in yrs (95%CI)

at gonadarche 11.6 (11.5-11.7), testicular volume ≥ 4mL 11.6 (11.5-11.8), pubarche 12.2 (12.1-12.4)) [Sørensen et al., JCEM 2009]. Baseline clinical assessment of pubertal development by Tanner staging including testis volume using a Prader orchidometer was performed by trained physicians in 244/254 boys. Timing of pubertal milestones was estimated by probit analyses.

Results: Age at pubertal onset was similar between obese boys (zBMI >2SD) and overweight controls (zBMI >1SD and ≤2SD): mean (95% CI) gonadarche at 11.6 yrs (11.3-11.9) vs 11.5 (11.1-11.9) yrs, p=n.s.; testicular volume ≥ 4mL at 11.2 (11.0-11.5) vs 11.4 (11.0-11.8) yrs, p=n.s.; and pubarche at 11.9 (11.5-12.3) vs 11.8 (11.3-12.3) yrs, p=n.s., respectively. In the obese cohort, median (range) zBMI at Tanner staging was 3.2 (2-6.3). In obese boys, zBMI was not associated with onset of any of pubertal milestones.

Conclusion: We demonstrate that obesity in boys is not associated with delayed pubertal timing compared to overweight boys. However, it appears that the strong negative association between BMI and age at pubertal onset that is usually observed in boys within the normal BMI range, is attenuated in obese boys.

P1-115

Mutation screening of the Sonic Hedgehog signaling-related genes in 120 Japanese patients with congenital hypopituitarism

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Introduction: The Sonic hedgehog (SHH) signaling pathway plays a crucial role in development of the forebrain and pituitary. Mutations in SHH signaling related genes are well known to be the cause of Holoprosencephaly (HPE), which results from developmental field defect or impaired midline cleavage of the embryonic forebrain, and is frequently associated with hypopituitarism. This study aimed to define the prevalence of congenital hypopituitarism (CH) in terms of seven SHH or HPE-related genes (*GLI2*, *SHH*, *TGIF1*, *SIX3*, *ZIC2*, *GPR161*, and *CDON*) among Japanese patients.

Subjects and Methods: We enrolled 120 (among them, 32 patients with midline defect) Japanese CH patients. The inclusion criteria were as follows: 1) short stature with severe GH deficiency (GH peak < 3 ng/mL) confirmed by hypoglycemic provocation test, or inadequate low serum GH at a time of severe hypoglycemia as neonate, and 2) anterior pituitary hypoplasia as detected by brain MRI. We sequenced all coding exons and flanking introns of 7 genes (*GLI2*, *SHH*, *TGIF1*, *SIX3*, *ZIC2*, *GPR161*, and *CDON*) by PCR-direct sequencing or next generation sequencing methods. The gene regulatory properties of mutant *TGIF1* proteins were characterized *in vitro*.

Results: We identified a novel *TGIF1* mutation, namely p.N235Y in one CH patient with cleft palate, and one recurrent *TGIF1* mutation, namely p.R219C in non-syndromic CH patient.

We also identified two novel *GLI2* mutations in CH patients with or without midline defects. In vitro experiments showed that N235Y TGIF1 resulted in a decrease of repressing activity in Luciferase assay. Western blotting and subcellular localization revealed no significant difference between wild type and N235Y TGIF1. Electrophoretic mobility shift assays showed that the N235Y TGIF1 bound with slightly low efficiency to the wild type.

Discussion: The frequency of SHH or HPE-related gene mutations in patients with CH was 3.3% (4/120).

P1-116

How to Approach Systemic Hypersensitivity reactions to Gonadotropin Releasing Hormone Analogues during treatment of Central Precocious Puberty

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Background: Hypersensitivity reactions to gonadotropin releasing hormone analogues (GnRHa) is a rare but serious side effect. Besides, local reactions, urticaria, anaphylaxis, serum disease, Henoch Schonlein Purpura (HSP) have been reported during GnRHa treatment. Clinicians should be aware of the potential association of GnRHa with systemic hypersensitivity reactions.

Case Reports: Here, we report nine girls with systemic hypersensitivity reactions to GnRHa among 232 patients with precocious puberty receiving GnRHa treatment in a time period of 3 years (3.8%). Six patients had type 1 hypersensitivity reaction (generalised hives, pruritus, and/or edema) to triptorelin acetate (TA), two patients to leuproide acetate (LA), and one patient to both medications who also developed anaphylaxis to LA during intradermal skin prick test. Another patient had purpuric skin reactions which was consistent with HSP. GnRHa treatment was discontinued in two patients (due to anaphylaxis in one and, refusal to continue treatment in the other). Treatment was changed to the other GnRHa preparation (n=6), or was continued with the same medication with premedication of antihistamines and corticosteroids before GnRHa injection (n=1) due to unavailability of alternative GnRHa at that time. None of the patients developed new reactions after these precautions.

Based on our experience, the following algorithm is proposed for systemic hypersensitivity to GnRHa treatment: After the exclusion of other potential etiological factors, if GnRHa related allergy is likely, we suggest to switch to alternative GnRHa under medical supervision. If there is no reaction to alternative GnRHa continue with that. If there is reaction with alternative GnRHa we perform

skin prick test (SPT) and intradermal test (IDT). If no reaction is detected to the active medication; we suggest to continue with same GnRHa with premedication. If SPT and IDT shows reactivity to active medication and if treatment is mandatory we suggest desensitization, or else stopping the GnRHa.

Conclusion: Systemic hypersensitivity reactions should be evaluated carefully during GnRHa treatment and cross reaction to the other GnRHAs should be kept in mind. The proposed algorithm is useful to manage such cases. Any kind of skin reaction need to be evaluated carefully in cases of GnRHa.

P1-117

The Role of Rat Hypothalamus Kisspeptin, Neurokinin and their respective Receptors in the Prolactin-Infertility Interaction

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Aim: In this study, we investigated whether there was a relationship between prolactin hormone (PRL), whose excess levels lead to infertility, and expression of Kisspeptin (Kiss1), Neurokinin (Tac2) and their respective Receptors.

Material and Methods: In our study, 12-16 weeks old 40 female Wistar Albino rats were classified into three groups; control group (n=10), physiological saline (SF) (n=10), and metaclopramide group (n=20), with high prolactin levels. Blood prolactin levels of all groups were measured using the ELISA immunoassay kit after two weeks of administration. Kiss1, Kiss1 Receptor (Kiss1R), Tac2, Tac2 Receptor (Tac2R) genes RNA expression were measured from hypothalamus.

Results: We found that prolactin level was highest in Metaclopramide group and lowest in the control group. When prolactin levels were compared in groups, a statistically significant difference was found between the groups ($p < 0.001$). In Group 3, where PRL levels increased, the expression values of Kiss1, Kiss1R, and Tac2 genes were significantly decreased compared to the other two groups ($p < 0.001$). There was no statistically significant difference between the groups in terms of expression values of Tac2R gene ($p = 0.052$). However, it can be inferred that this difference between the groups was borderline significant depending on the value of p .

Conclusion: In light of our findings, we think that prolactin increase may have adverse effects on reproduction by means of neuropeptides and our study will contribute in understanding the molecular basis of infertility problems caused by increased prolactin levels.

P1-118**Whole Exome Sequencing (WES) reveals oligogenic gene mutations in a case of Combined Pituitary Hormone Deficiency (CPHD)**

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Introduction: CPHD is characterized by GH and at least one other pituitary hormone deficiency. Mutations in genes expressed in the developing head, hypothalamus, and/or pituitary cause CPHD. To date around 30 genes have been identified to be related to CPHD, however the 85% of the cases remain with unknown aetiology. Whole Exome Sequencing (WES) enables parallel searching for pathogenic variants of CPHD in targeted known gene panels as well as the identification of novel genes related to CPHD thus allowing genetic diagnosis, prognosis and genetic counseling.

Patient and Methods: A newborn boy (46, XY) delivered by CS due to IUGR with a birthweight of 2200gr, presented with refractory hypoglycemia and mild hypotonia. On physical examination he had micropenis with bilaterally palpable small testes. Endocrinological work up revealed secondary hypothyroidism, secondary adrenal insufficiency and hypogonadotropic hypogonadism (HH). MRI scan of the hypothalamic pituitary region depicted hypoplastic anterior pituitary and ectopic posterior pituitary lobe with absence of pituitary stalk.

WES was carried out on an Ion Torrent S5 platform and the data was aligned to the human genome reference hg19 with Torrent Mapping Alignment Program (TMAP) and annotated by the Ion Reporter software and Varafit. An *in silico* panel of 80 genes related to CPHD was employed to search for variants with MAF values <1%. The pathogenic variants selected were verified by Sanger sequencing.

Results: Three heterozygous pathogenic variants were detected to be related to the patient's phenotype in three genes: *BMP4*; p.A42P (maternally inherited) related to CPHD, *GNRH1*; p.Arg73X (paternally inherited) related to HH and *SRA1* p.Q32E related to HH and secondary adrenal insufficiency.

Conclusions: We speculate that a synergistic action of several gene mutations may underlie our patient's phenotype.

BMP4 plays significant role in early organogenesis, pituitary development and function. The variant p.A42P, has been previously described in a patient with tooth agenesis, however a heterozygous *BMP4* mutation (p.R300P) has been reported in a case with CPHD and hypoplastic pituitary gland. The pathogenic variant p.Arg73X of the *GNRH1* gene has been previously described in a patient with HH. *SRA1* (Steroid Receptor Activator) is a functional ncRNA which among its other functions regulate steroid receptors-dependent gene expression. The pathogenic variant p.Q32E has previously been identified in a patient with HH and could probably explain the secondary adrenal insufficiency of our patient, since *SRA1* regulates SF1 target gene expression by functioning as a coactivator in association with DAX1.

P1-119**Menarche and its relation to the pubertal growth spurt**

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Background: Both timing of menarche and growth patterns have changed with time (secular changes), highlighting the need of updated knowledge in this topic¹. Questions how growth is related to menarche are common in pediatric/pediatric endocrine outpatient clinics. The QEPS-growth model makes it possible to conduct detailed analyses of pubertal growth².

Objective: To investigate the relationship between the timing of menarche and pubertal growth, specifically to analyse when menarche occurs related to the pubertal growth spurt and how the pubertal height gain is related to the timing of menarche.

Method: Pubertal growth was analysed and related to the timing of menarche in a longitudinally followed population, the GrowUp₁₉₉₀Gothenburg cohort (community-based setting)³. The analysed study group included 865 females. Analyses of the growth patterns were done with the QEPS growth model². Information of the timing of menarche for each study subject were related to individual growth functions from the QEPS model. The timing of menarche was related to the percentage of specific pubertal gain attained (*P%*) and the total pubertal height gain (*TgainP5-95*).

Results: Menarche occurred in the mean at the time when around 60% of the specific pubertal gain was reached. Mean menarcheal age was 12.85 years (standard deviation 1.58 years) There was a negative linear correlation between the timing of menarche and the total pubertal height gain; in mean 28.7, 26.7 and 25.2 cm for girls with early (8-11 years), average (12-14 years) and late menarche (15-19 years) respectively. The difference in height gain was due to more Q function growth in girls with early menarche.

Conclusion: In a cohort of healthy Swedish girls with longitudinal growth data born in the 1990s, menarche was seen when around 60% of the specific pubertal height gain was achieved. The later the age of menarche, the less pubertal height gain. There is a broad variation in pubertal growth, where menarche is one important factor for different growth patterns around puberty in girls.

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P1-120

Role of priming in peri-pubertal growth delays: preliminary results of a large multicenter study

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Introduction: Peripubertal children with delayed puberty frequently display a poor growth rate prompting endocrine work-up. Whether priming with sex steroids should routinely be performed in these patients to improve specificity of growth hormone stimulation tests (GHST) is unclear. Treatment with sex steroids in constitutional delay of growth and puberty (CDGP) is also debated.

Patients and Methods: This multicenter retrospective study included 151 normal weight children (54 females) presenting with pubertal delay and short stature/poor growth rate (aged 12.55 ± 1.82 years). Patients were diagnosed as CDGP if GH peak after a GHST was $\geq 8 \mu\text{g/L}$ or isolated growth hormone deficiency (IGHD) if $< 8 \mu\text{g/L}$. CDGP patients received low-dose sex steroids (LDSS) for 3-51 months, or no treatment. All IGHD patients received rhGH (25-35 $\mu\text{g/kg/day}$). Within the IGHD cohort, 77/85 were retested at final height (FH). Patients were divided into 6 groups: untreated CDGP diagnosed with or without priming (1A n = 31; 2A = 21), CDGP receiving LDSS diagnosed with or without priming (1B = 12; 2B = 2), IGHD diagnosed with or without priming (1C = 42; 2C = 43). Standard deviation score (SDS) FH, Δ SDS FH - SDS target height (TH) and degree of success (defined as $-1 \leq \Delta$ SDS FH - SDS TH ≤ 1) were outcomes of interest.

Results: SDS FH was higher in group 1C than 1A (-0.86 vs -1.43 , $p = 0.014$) and similar trend was found for Δ SDS FH-TH (1C -0.07 vs 1A -0.74 ; $p = 0.005$). SDS FH and Δ SDS FH-TH were comparable between groups 2C and 2A (-0.93 vs -0.99 , $p = 0.85$; -0.31 vs -0.46 , $p = 0.508$).

IGHD patients showed the highest degree of success [group C (1C + 2C) 89% vs group B (1B + 2B) 86% vs group A (1A+2A) 63% $p = 0.0009$], and above all group 1C (1C 93%, 2C 86%, 1B 83%, 1A 68%, 2A 57%, $p = 0.005$).

At retesting, a higher proportion of permanent IGHD was documented in group 1C (1C 27% vs 2C 17.5%; N.S.), not reaching statistical significance possibly due to low sample size.

Conclusion: Our data suggest that priming with sex steroids in peripubertal short subjects improves the ability to select those patients who would more likely benefit from rhGH therapy. Indeed, rhGH treatment in IGHD seems to give advantages in terms of final height compared to untreated CDGP especially in those patients diagnosed upon a primed GHST.

Sex Differentiation, Gonads and Gynaecology or Sex Endocrinology

P1-121

Lower urinary tract dysfunction and infection in girls with disorders of sex development and urogenital sinus

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Introduction: Two-stage surgical feminization is a part of the multidisciplinary rehabilitation of girls with external genital virilization. The first stage involves clitoroplasty and labioplasty with preservation of urogenital sinus (US) in girls with third degree of virilization according to Prader classification and higher. US eliminating is performed by second stage in the puberty. Persistence US may cause dysfunction of urodynamics and infections of the lower urinary tract

Aim: To assess the functional state of the lower urinary tract in girls with disorders of sex development (DSD) and US.

Materials and Methods: The study included 35 girls and women from 11 to 32 years old with DSD with US. Most of them have congenital adrenal hyperplasia (32), fewer girls have partial gonadal dysgenesis (1) and idiopathic virilization (2). Patients were examined before second stage surgical feminization in 5-19 years after the first stage. Concomitant pathology of the urogenital tract was detected in 23 (65%) patients. Urinary tract infection was verified in 17 (48%) base on anamnesis and changes in urine tests. Cystoscopy was performed part of patients with US, but in all cases revealed signs of chronic urinary tract infection presented as follicular, granular cystitis and bladder mucosal metaplasia. Bladder dysfunction was diagnosed in 5 (14%) as stress urinary incontinence, enuresis and hyporeflex bladder base on history, urination rhythm and analysis of questionnaire ICIQ-SF on urinary incontinence influence on quality of life. Trapped menstrual secretions presented as hematometra, hematocolpos, and urine accumulation and stagnation in the vagina in anamnesis or as a

result of preoperative studies were diagnosed in 10 (28%). Part of these girls (6) with hematometra/hematocolpos previously were operated yet. One of them was operated twice. Combination of the listed complications were observed in five patients (14%).

Conclusion: Urogenital sinus in girls with DSD, which was observed in all examined patients, is a risk factor for the development of urinary tract infection, hydrocolpos/hydrometra disorders and bladder dysfunction. This circumstance requires change in surgical feminization tactics in girls with disorders of sex development, taking into account the anatomical components of genitalia malformations.

P1-122

Abstract withdrawn

P1-123

Does the internet provide accurate and valid health information regarding disorders of sex development?

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Background: The internet provides a multitude of health information. Understanding disorders/differences of sex development (DSD) can be difficult for families partly due to their complexity and relatively low prevalence. Consequently, families may use the internet to gain understanding of their child's condition, however the quality of this information has not been formally assessed.

Aims: To assess the quality, validity and accuracy of website health information concerning commonly searched terms related to DSD.

Methods: Our multi-professional DSD Team and parents of current patients at Bristol Royal Hospital for Children were consulted to understand commonly searched terms. Five search terms were selected "Disorders of Sex Development OR Differences of Sex Development", "Congenital Adrenal Hyperplasia" (CAH), "Ambiguous Genitalia OR Atypical Genitalia", "Cliteromegaly OR Clitoromegaly" and "Micropenis". The top 20 Google searches were scored by two independent reviewers using the validated QUality Evaluation Scoring Tool (QUEST). The tool scores 6 domains (Authorship, Attribution, Conflict of Interest, Currency, Complementarity and Tone) with 28 the maximum score. Only websites meeting the inclusion criteria: article/information-like leaflet format, in English, no payment/login required, and articles

considering aetiology/diagnosis/treatment of disorder were included.

Results: Inter-rater reliability demonstrated substantial agreement across all domains (Cohen's kappa=0.71-0.83) except 'Tone' (Cohen's kappa=0.55, moderate agreement). Thirty-two percent of searches were excluded due to the website either being a tabloid article (6%, only with micropenis searches), in an inappropriate format (10%) or the site had a paywall (16%). There were no significant differences in scores across all 5 search terms; DSD (n=14, mean=18.7 SD=5.6), CAH (n=14, mean=16.7, SD=3.4), Ambiguous Genitalia (n=14, mean=14.1, SD=4.9), Cliteromegaly (n=12, mean=19.6, SD=6.0) and Micropenis (n=12, mean=17.2, SD=7.4). There was no evidence that overall QUEST score was related to search rank. There was evidence that average scores were related to website category with hospital websites scoring the lowest. Compared to hospital websites (n=21, mean score=11.8) scores from health information e.g. Healthline (n=17, mean score=18, p=0.001), general information e.g. Wikipedia (n=4, mean score=21, p=0.003), peer reviewed publication (mean score=22.1, p<0.001) websites were significantly higher.

Conclusion: Our study demonstrates further validation of the QUEST Tool with good interindividual agreement. A high proportion of articles searched are either not accessible or from tabloid sources. The more colloquial term 'Micropenis' produced variable information quality. The lowest quality information came from hospital websites and we would recommend professionals considering the quality criteria in the QUEST tool when designing health information websites.

P1-124

A human model showing the ability of testis XX cells to masculinise into Sertoli cells and success of microTESE surgery in paediatric azoospermia

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In the typical developing gonad, cells with XY chromosomes become masculinised into Sertoli cells, leading to the development of the bipotential gonad into testes. Disruptions to sex determining genes and transcription factors, or XX chromosome complement, typically leads to failure of Sertoli cell development. In the study of sex determination, upregulation of specific genes in animal models has successfully led to male factor expression in XX cells in some animals but not in others. There have been no previous reports of

XX cells expressing male factors or Sertoli characteristics in the human.

We report a phenotypically normal boy with a 46,XX/46,XY tetragametic chimeric karyotype. Chromosomal microarray confirmed four distinct SNP profiles in the one individual, ie. fusion of four distinct gametes (X, X, Y, Y). He commenced puberty at age 13, and spontaneously reached Tanner stage 3 puberty with 10 mL testes. Unfortunately he began to show testicular failure from age 15, with FSH rising to 28 u/L and testes reducing to 6mL bilaterally.

Ejaculate was collected for semen analysis and storage, but found azoospermia. The patient then underwent microdissection testicular sperm extraction (microTESE) as the most advanced technique currently available to optimise preservation of any remaining fertility, along with testicular biopsy for gonadal analysis. MicroTESE surgery is becoming the gold standard for sperm retrieval in azoospermia, with key applications in individuals with disorders of sex development, and was successful in finding sperm for storage.

Histologic and FISH cytogenetic analysis of the testicular biopsy revealed very interesting results, confirming for the first time the ability of XX cells to masculinise into Sertoli cells in the human testis. As the peripheral blood XX cells had a normal profile on microarray, it was assumed the testicular XX cells also contained a normal genetic complement. This suggests possible endocrine or other epigenetic influences on the fundamental mechanism of sex determination, as opposed to a process solely dependent on the endogenous DNA profile of the individual cell nucleus. RNA analysis of the XX Sertoli cells is underway.

Here we show for the first time that that XX cells are able to masculinise into phenotypically normal Sertoli cells in the human testis, illuminating new possible mechanisms of paracrine or epigenetic effects on sex determination. We also show that paediatric use of microTESE surgery can be successful in cases of azoospermia, and may significantly improve the fertility prospects for many young people with DSD.

P1-125

A Health-Related Quality of Life Tool for Parents of Young Children With Disorders of Sex Development

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Background: Disorders of sex development (DSD) may be associated with adverse psychosocial and psychosexual outcomes in adults. However, there is a paucity of information on health-related quality of life outcomes in parents and young children with DSD.

Objective: To evaluate the use of parent-reported outcome (PRO) questionnaires that can be routinely used in the outpatient setting to assess the impact of DSD on parents and children.

Methods: Previously validated DSD-sensitive and generic PRO items were combined to develop a Parent Self-Report questionnaire and a Parent Proxy-Report questionnaire for children under 7 years of age. Questionnaires were completed by parents of 65 children attending DSD and endocrine clinics at one tertiary paediatric hospital in Scotland.

Results: Ninety-four questionnaires were completed. Mothers of children with DSD reported significantly greater 'Future concerns' (median SDS -0.3; IQR -1.0–0.2) than parents of children with other endocrine conditions (median SDS 1.2; IQR 0.6-1.7), P<0.01. Similarly, fathers of children with DSD report greater 'Future concerns' (median SDS -1.3; IQR -3.1–0.2) than parents of children with other endocrine conditions (median SDS 0.5; IQR 0.2-0.9), P<0.01. Mothers of children with DSD also reported a greater degree of apprehension when 'Talking to others' about their child's condition (median SDS 0.19, IQR -0.6-1.0 versus median SDS 0.7, IQR 0.04-1.3), P=0.03. There was no significant difference in symptoms of psychological distress, as assessed via the PHQ-4 scale, between parents of children with DSD (median PHQ-4 score median 0; IQR 0.0-2.0) and endocrine conditions (median PHQ-4 score 0; IQR 0.0-2.0), P>0.05. Time to completion of both questionnaires was less than 10 minutes and questionnaire acceptability was 100% amongst parents.

Conclusion: The use of brief PRO tools in parents and young children with DSD is an acceptable practice and can be routinely used in the outpatient setting to assess and monitor parent and patient needs. DSD was associated with greater parental concerns over the child's future than other endocrine conditions and highlights opportunities for targeted intervention.

P1-126

Longitudinal Changes In External Masculinisation Scores In Boys With XY Disorder Of Sex Development (DSD)

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Introduction: Although, there are several studies that use the external masculinisation score (EMS) for numerical description of the external genitalia in infants with DSD, data on change in EMS in the routine clinical setting are lacking.

Objectives: To determine the longitudinal change in EMS and its determinants in a cohort of boys with XY DSD in one specialist centre.

Methods: Observational study of boys with XY DSD who were evaluated by the DSD Diagnostic Board in Glasgow from 2010 to 2018. Calculations of EMS at initial (EMS1) and most recent (EMS2) assessments were performed based on information obtained from medical records. Surgical interventions (SI) including orchidopexies, hypospadias repairs, biopsies and orchidectomy and therapeutic interventions (TI) including testosterone therapy were also recorded.

Results: 171 boys with median age at initial and last assessment of 0.82yrs (range, 0.00, 16.73) and 4.67yrs (0.23, 19.05), respectively, were identified. Median follow-up time was 3.2yrs (0.08, 16.13). Median EMS, out of 12, at first and last assessment was 8.5 (2, 12) and 10.5 (3, 12), respectively ($p<0.0001$). Median change in EMS was 1.5 (-2, 9) with a median change of 0.49/yr (-1.21, 5.53). Of the 171 boys, 133 (78%) had an EMS2 higher than EMS1 with median change of 2 (0.5, 9) and median duration of follow-up of 3.76yrs (0.18, 16.13). There were 29 (17%) boys who had no change in EMS over the median follow-up period of 1.29yrs (0.08, 4.82). Of these 29 boys, 18 (62%) were waiting for surgery, in 8 (28%) no surgical intervention was required and 3 (10%) had a combination of orchidopexy with contralateral orchidectomy or testicular atrophy. In the remaining 9 (5%) there was a decrease in EMS by a median value of 0.5 (2, 0.5) over a median follow-up period of 4.7yrs (1.42, 14.05) and in all 9 there was a history of orchidectomy or spontaneous atrophy. SI were evident in 148 (87%) boys whereas TI were recorded in 10 (6%). There was no significant change in EMS in those who had TI and had no SI. A median EMS1 of 8 (2, 11.5) rose to 11 (3, 12) in the 161 (94%) boys who did not have any TI ($p<0.001$).

Conclusions: The EMS in boys with XY DSD improves over childhood and adolescence. The change in EMS in boys with DSD is poorer in those who do not have surgery and who are hypogonadal and require TI.

P1-127

Mutations in CBX2 associated with gonadal anomalies in 46,XY and 46,XX individuals

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The Polycomb Repressive Complex 1 (PRC1) represses gene expression through CBX2, which binds to H3K27me3 and promotes chromatin expression. Recently, CBX2 has been shown to function in testis-formation by directly repressing Wnt4's downstream target, *Lef1*, in Sertoli cells rather than positively controlling *Sry* expression, as previously thought. Here, we describe two new cases carrying missense mutations in CBX2. The first is a female with 46,XY complete gonadal dysgenesis and the second is a 46,XX individual with intellectual deficiency, facial dysmorphia, a small uterus with no ovaries. In an exome sequencing approach, the former patient was found to carry a *CBX2*, c.G404A mutation that is predicted to result in an p.R135Q amino acid change, whilst the latter patient carried a *CBX2*, c.G1339A mutation that is predicted to result in an p.G447R amino acid change. Both mutations are predicted to be damaging to the protein by multiple prediction tools. The p.R135Q mutation is absent from all public SNP data-

bases and the p.G447R change has been reported in gnomAD at a minor allelic frequency of 6.6×10^{-5} in South Asian populations. Analysis of our exome data and public SNP databases also indicate that the smaller CBX2 isoform 2.2 is unlikely to be functional as healthy controls carry multiple loss-of-function mutations in this isoform. Mice lacking *Cbx2* have been reported to have small ovaries associated with a spectrum of meiotic anomalies in germ cells and our data suggest that mutations in the human *CBX2* gene could be a novel cause of ovarian insufficiency as well as 46,XY gonadal dysgenesis.

P1-128

The novel founder homozygous V225M mutation in the 17HSDB3 gene causes aberrant splicing and severe XY-DSD

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Background: Mutations in the gene HSD17B3 encoding the 17-beta hydroxysteroid dehydrogenase 3 enzyme cause testosterone insufficiency leading to XY DSD. In this study the clinical characteristics and molecular etiology of 3 new severe XY DSD cases from consanguineous families are elucidated.

Clinical Report: Three female patients (2 sisters and a single unrelated female) presented at ages 0.1, 8 and 0.7 years with ambiguous or complete external female genitalia. All 3 had palpated gonads in the inguinal canal, consistent with testes in imaging studies and XY Karyotype. Endocrine workup showed normal cortisol and mineralocorticoid levels with a low testosterone/ androstenedione ratio. Urine metabolom for ketosteroids in the third female ruled out 5 alpha reductase dysfunction, and the mutation in 17HSDB3 gene was found by sequencing the gene.

Molecular Studies: Whole exome sequencing, carried out in both sisters and parents, revealed a homozygous novel mutation in the HSD17B3 gene - c. 673G>A, p. V225M. The same mutation was found by Sanger sequencing in the third unrelated patient. Haplotype analysis of a 4Mb region surrounding the HSD17B3 gene on chromosome 9 using short tandem repeat markers revealed that the mutation resides on the same allele in all 3 patients. The mutation was found to affect the splicing as Gel electrophoresis of RT-PCR products from one of our patients' testes cDNA revealed the expected 347bp amplicon, when using primers from exons 9 and 11, but also a shorter transcript of only 196bp. Sequencing of the shorter amplicon showed that this transcript did not include exon 10. Using capillary electrophoresis, we demonstrated that the relative proportion of transcripts retaining exon 10 to transcripts skipping exon 10 in the cDNA of healthy testes compared to affected testis was substantially (9.8x) higher. The

disruption of the tightly regulated splicing of an exon may result in an imbalance in the relevant protein isoforms and lead to the significant testosterone deficiency.

Conclusion: The founder novel homozygous c. 673G>A, p. V225M mutation in the 17HSDB3 gene causes severe XY-DSD. Other than changing a conserved amino acid residue this mutation alters 17HSDB3 gene transcription by skipping exon 10 and thereby contributing to significantly decreased 17HSDB3 enzymatic activity.

P1-129

Molecular diagnosis of patients with 46,XY differences in sex development in a single tertiary center

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Disorders/differences in sex development (DSD) are defined as congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical. 46,XY DSD include defects in androgen synthesis or action or complete (CGD)/partial (PGD) gonadal dysgenesis. The aim of this study was to characterize the molecular genetic diagnosis of individuals with 46,XY DSD followed at Garrahan Pediatric Hospital.

Medical records of 140 patients (P) followed at the Endocrinology Department because of 46,XY DSD were reviewed. DNA samples were obtained in 84/140. Subjects were divided into 3 groups based on clinical characteristics, hormonal measurements, gonad histology and ultrasound/laparoscopic findings: defects in androgen synthesis (group 1, G1 n=8) or action (group 2, G2 n=34) and CGD/PGD (group 3, G3 n=40). First, candidate gene sequencing was performed: in G1 *StAR*, *CYP17A1*, *HSD3B2*, *POR* or *SRD5A2*; in G2 *AR* and in G3 *SRY*, *NR5A1* and/or *WT1*. Copy number variations (CNVs) of *SRY*, *SOX9*, *NR0B1*, *NR5A1* and *WNT4* were assessed by MLPA in G3, both in DNA from peripheral blood leukocytes and, when available, gonadal tissue. In this group, a panel of 35 genes known to cause XY DSD or known to play a role in gonadal differentiation and genitourinary tract development was designed for next generation sequencing (NGS). Moreover, whole exome sequencing (WES) was conducted in the remaining undiagnosed individuals. Every clinically significant variant was confirmed by Sanger sequencing in proband and parents to elucidate inheritance pattern.

In G1, deleterious gene mutations were detected in *StAR* (n:1), *CYP17A1* (n:1), *HSD3B2* (n:2), *POR* (n:2) and *SRD5A2* (n:2). In G2, *AR* mutations were found in 22 subjects of 14 families (F). In G3, mutations were found in *SRY* (2 siblings), *NR5A1* (n:7 F) and *WT1* (n:9). No CNVs were found by MLPA in peripheral blood or gonad DNA. The designed gene panel allowed the diagnosis of

4 P in whom mutations in *ZFPM2* gene were found. WES analysis revealed mutations in *DHX37* gene in 2 P.

In this cohort, excluding enzymatic defects, molecular characterization was reached in approximately 43% (36/84). Diagnosis in 46,XY DSD can be challenging due to overlapping clinical characteristics or poor genotype/phenotype correlation. Thus, candidate gene sequencing strategy might not be adequate in all cases. NGS can be a better approach to reach an etiologic diagnosis reducing time and medical interventions. However, other etiologies should be considered: non coding genomic regions, oligo/multigenic inheritance, epigenetic pathways or environmental factors.

P1-130

In vivo and In vitro study of 17 β estradiol against amyloid beta neurotoxicity in synaptosomes of aging female rats : A therapeutic potential drug for Parkinson's disease

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Objectives: The aim of the present study was to determine the effects of neuropeptide, neuropeptide B (NKB) and amyloid beta fragment A β (25-35) on 17 β estradiol (E2) treated aging female rat brain of 3 months (young), 12 months (adult) and 24 months (old) age groups.

Methods: The aged rats (12 and 24 months old) were given subcutaneous injection of E2 (0.1 μ g/g body weight) for 30 days. Synaptosomes were incubated with NKB, A β (25-35) and NKB+A β (25-35) in a microfuge tubes at 37°C for 60 min in a shaking water bath with 0.1, 1 and 5 μ M concentration of each of the peptides in all age groups of control and E2 treated rats. The learning and memory function were assessed by Morris water maze test. The mRNA and protein levels of PPAR γ were evaluated by real time (RT)-PCR and Western blot analysis.

Results: The results obtained in the present work revealed that increased activities of antioxidant enzymes (glutathione reductase, superoxide dismutase and decrease in calcium levels, acetylcholinesterase (AChE) activity, neurolipofuscin accumulation and malondialdehyde (MDA) in presence of NKB and combined NKB and A β in vivo E2 treated aging rat brain. An *in vitro* incubation of E2 treated synaptosomes with A β showed toxic effects on all the parameters, while NKB showed stimulating effects and the combined NKB and A β showed a partial effects as compared to A β (25-35) and NKB alone. Similar results were obtained with the increased antioxidant enzymes levels, improved learning and memory performances, reduced AChE activity and MDA levels, significantly increased PPAR γ expression, and alleviated TNF- α , IL-1 β , and IL-6 compared with the E2 treated aging rat hippocampus.

Conclusion: Present study elucidates an antioxidant, anti-aging and neuroprotective role of tachykinin peptide NKB against the beta amyloid induced toxicity in E2 treated female rats.

P1-131**Is there the relationship between anxiety and depression level and clinical presentation of polycystic ovary syndrome in adolescent girls?**

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Background: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorder of the young women, and it could influence both physical and psychological wellbeing. As a consequence of obesity and hirsutism lower sexual attractiveness, higher emotional distress as well as higher depression score is frequently observed.

Study Objective: Was to evaluate anxiety and depression score as well as the body esteem and stress perception in adolescent girls with clinical features of hyperandrogenism (menstrual disorders and/or hirsutism).

Design & Participants: In 74 adolescent girls 1. Hospital Anxiety and Depression Scale (HADS), 2. Body Esteem Scale (BES, assessing Sexual Attractiveness, Weight Concern and Physical Condition), and 3. The 10-item Perceived Stress Scale (PSS-10) was carried out. According to clinical features of hyperandrogenism (menstrual disturbances, hirsutism), the study group was divided into three subgroups: G1 - 32 adolescent girls with diagnosed PCOS (chronological age 16.6 ± 1.0 y, gynecological age 52.8 ± 19.1 mo, BMI z-score 1.0 ± 1.1), G2. - 15 adolescent girls with idiopathic hirsutism (chronological age 16.0 ± 1.3 y, gynecological age 56.2 ± 18.4 mo, BMI z-score 1.2 ± 1.0), G3 - 27 healthy girls without menstrual disturbances or hirsutism (chronological age 16.0 ± 1.2 y, gynaecological age 37.5 ± 19.4 mo, BMI z-score 1.0 ± 1.0).

Results: In G3 the anxiety score was the highest (9.8 ± 3.2 score), compering to G1 (8.7 ± 2.9 score) and G2 (8.5 ± 4.3 score), but the difference did not reach the level of statistical significance. In all three study subgroups similar depression score was observed ($p > 0.05$). The depression score was negatively related to BMI z-score in G1 ($r = -0.4$, $p < 0.05$) and positively to testosterone level in G2 ($r = 0.6$, $p < 0.05$). There was negative correlation between anxiety score and DHEAS concentration in G2 ($r = -0.8$; $p < 0.01$). No significant differences in BES and PSS-10 score were observed between the study subgroups ($p > 0.05$). In G1 the perceived stress score as well as Weight Concern were negatively related to BMI z-score ($r = -0.7$, $p < 0.001$; $r = -0.5$, $p < 0.05$, respectively). Moreover, there was significant relationship between Weight Concern and hirsutism score ($r = 0.4$; $p < 0.05$) and between Sexual Attractiveness and testosterone level ($r = 0.4$; $p < 0.05$) in this subgroup. The perceived stress score correlated negatively with androstenedione level ($r = -0.6$; $p < 0.05$) and 17OHprogesterone concentration ($r = -0.8$; $p < 0.01$) in G2. The Weight Concern also in this group was related to BMI z-score ($r = -0.7$; $p < 0.01$).

Conclusions: In adolescent girls clinical features of hyperandrogenism are not connected with increased anxiety and depression level. However biochemical hyperandrogenism could significantly influence the perceived stress and body esteem.

P1-132**What is the recurrence rate of benign ovarian tumors in childhood? Ovarian Benign organic Tumors (OBT) are a rare pathology in childhood that require conservative surgery with an unknown risk of recurrence**

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Aim: The aim of the study was to predict the risk of tumor recurrence in OBT.

Material and Methods: We conducted a retrospective, observational study (2001-2018) on the management of OBT in girls aged 0 to 18 at Toulouse University Hospital, France.

Results: 68 patients were included. 16% were prepubertal. Mean age was 11.35 ± 3.08 years. Pain was the main symptom in 49% of patients. 10 patients (mainly prepubertal) had acute ovarian torsion. The diagnosis was confirmed in all cases by pelvic ultrasound showing ovarian tumor and negative tumor markers. The evaluation was completed in 68 % of cases by MRI or CT.

Tumorectomy was performed in 70.6% of cases (48/68) and oophorectomy in 29.4%. Oophorectomy was more frequent in solid masses than in cystic masses: 36.96% (17/46) versus 10% (2/20), $p = 0.026$.

Laparoscopic surgery was performed in 28% of cases.

There were 62% germ cell tumors and 38% epithelial tumors.

Mean postoperative follow-up was 3.4 ± 2.6 years with 7 visits. 10.3% of patients ($n = 7$) had a recurrence on average 17 months (range 2 to 43 months). The solid ultrasound appearance and the bilaterality appeared to increase the risk of recurrence but no predictive factor was found. Puberty progression was age-appropriate for 97% of patients.

Conclusion: In our series, the recurrence rate after the first OBT is evaluated at 10%. The monitoring for at least 3 years is therefore essential with a pelvic ultrasound every six months.

New prospective and multicenter studies, as well as the creation of a register of rare benign ovarian tumors in childhood, are necessary to improve the follow-up of these patients.

P1-133**Congenital Disorders of Reproductive Hormones in Mini-puberty Boys with Bilateral Cryptorchidism**

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Background: Cryptorchidism is associated with the high risk of infertility. In some cases it may be the one of the first symptom of congenital hypogonadism. The period of 0 – 6 month of life is a

short window for postnatal testicular maturation and the diagnostic of reproductive disorders.

Objective: To evaluate the functional condition of pituitary and gonads in mini-puberty boys with bilateral cryptorchidism.

Method: 28 boys ages 1–3 months with bilateral inguinal testes were examined. Control group consist of 40 healthy boys ages 1–3 month. Methods: Gonads evaluation and serum reproductive hormones in all boys were performed and included ultrasound and hormonal tests – gonadotropins, testosterone and inhibin B serum levels by immunoenzyme assays. Molecular assay was included in examination if it was necessary.

Results: Inguinal testes were found by ultrasound. Hormonal tests revealed different results: a) normal LH, FSH, testosterone and inhibin B level in 53,6% patients; b) increase the LH – 7.8 [6.0; 11.1] IU/l and FSH 15.9 [8.8; 19] IU/l ($p=0,0007$) level, normal testosterone – 5.0 (1.3; 5.4) nmol/l and decrease inhibin B level 96 [48; 97] IU/l ($P=0.023$) in 28,6% boys; c) low LH - 0,08[0,05; 0,12], FSH serum level, low testosterone and inhibin B – 39 [28; 43] ($p=0.003$) in 17,8% boys.

Conclusion: Hormonal investigation in mini-puberty boys with inguinal cryptorchidism showed a prognosis for puberty and fertility and it is the most important for hypogonadotropic hypogonadism early determination. Testicular disorders were revealed in 28,6% with bilateral cryptorchidism; the hypogonadotropic hypogonadism was diagnosed – in 14% boys with bilateral inguinal cryptorchidism.

P1-134

Targeted Panel Gene Sequencing for Identification of Genetic Etiology of 46,XY Disorders of Sex Development

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Background: Disorders of sex development (DSD) vary phenotypically and are caused by a number of genetic etiologies. Although several genetic abnormalities have been discovered through genetic analyses, the underlying genetic causes of 46, XY DSD remain unknown in most of the cases

Aim: To identify genetic defects in patients with 46,XY DSD.

Material and Methods: A total 76 DSD patients included in the study, 22 of these patients who were screened and did not carry mutations for SRD5A2 and AR genes and 54 patients suspected to have gonadal dysgenesis or androgen synthesis defects. 31 DSD associated genes were sequenced using in-house-designed next generation sequencing (NGS) targeted panel-gene and analyzed for gross deletion/duplication with MLPA (P185 and P334).

Results: 12 previously described and 22 suspected rare variants are identified in 15 different genes within a total of 32 cases, leading to a diagnostic rate to 40.5%. Highest rate of causative variants was identified in HSD17B3 (11.1%) which was followed by, NR5A1, LHCGR, DHH, ZFMP2, SR5A2, SOX9, WT1, POR, HOXA4, AMHR2, CYP5A, AR, MAP3K1 and GATA4. Genetic results led to a change of initial clinical diagnosis of some patients with androgen synthesis and androgen action groups and these patients were reclassified as disorder of gonadal dysgenesis.

Conclusion: Genetic analyses following clinical and hormonal evaluation is essential for the definitive diagnosis, management and counseling of patients and families with 46,XY DSD with a great phenotypic and genetic heterogeneity. NGS targeted panel gene seems to be a powerful tool to detect associated variants of DSD.

P1-135

Combining clinical and genetic approaches in diagnosing a large Brazilian cohort of patients with 46,XY Differences of Sex Development (DSD)

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Background: Most published studies on 46,XY DSD focused on genetic findings without association with biochemical work-up.

Objectives: To retrospectively analyze the clinical and genetic findings of a large cohort of 46,XY DSD patients.

Methods: 285 non-syndromic 46,XY DSD individuals (192 sporadic and 89 familial cases) were studied. LH, FSH, testosterone (T), androstenedione (A) were measured by immunoradiometric or immunofluorimetric assays and dihydrotestosterone (DHT) by RIA after *celite chromatography* or by liquid chromatography tandem mass spectrometry. Based on hormonal and imaging assessment, the patients were classified as: gonadal dysgenesis (GD; n= 60); androgen insensitivity syndrome [AIS; n= 61: 34 with complete AIS (CAIS) and 27 with partial AIS (PAIS) form]; defects in testosterone production [DTP; n= 81, includes SRD5A2 (n=37), HSD17B3 (n=17), CYP17A1 (n=15) and HSD3B2 (n=5) deficiencies and Leydig cell hypoplasia (n=7)]; persistent müllerian duct

syndrome (n=4) and DSD of unknown etiology (n=79). Sanger sequencing was performed in 90% of the patients and massively parallel sequencing was performed in 88 patients without a previous molecular diagnosis. The identified variants were classified according to the ACMG criteria.

Results: Pathogenic or likely pathogenic variants were identified in 20 GD patients (33%), in 50 (81%) AIS patients (94% of CAIS and 66% of PAIS), in 81 patients (95%) with DTP and in 20 patients (25.6%) with unknown etiology, including variants in gonadal development (n= 8), in AR (n=8), in SRD5A2 (n=2), in HSD17B3 (n=1) and in AMH (n=1) genes. Defects in NR5A1 and DHX37 were identified in 11 and 8 probands, respectively, being the most frequent cause of GD. Six patients with variants in gonadal development genes (five with NR5A1 and one with MAP3K1 variants) had preserved gonadal function and absence of uterus. Two post-pubertal patients with SRD5A2 defects had a normal T/DHT (reference 14±5.2) and 9% of patients (3/32) with other diagnosis had an altered ratio. A T/A ratio < 0.8 was observed in 17/18 of the patients with molecular diagnosis of HSD17B3 deficiency and also in 2/49 patients with other diagnoses, both patients were under 6 months of age and the ratio was obtained in baseline condition.

Conclusion: The molecular diagnosis was established in 55% of the 46,XY DSD individuals, mainly in patients with AIS and DTP, with a lower diagnostic yield in GD patients. Clinical assessment was accurate in most cases, however six cases of GD, two of SRD5A2 and one of HSD17B3 deficiencies would have been missed, emphasizing the importance of the molecular studies in diagnosing 46,XY DSD patients.

P1-136

Serum estradiol is associated with inhibin B in healthy 1-6 years old girls

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Background: The female gonadal axis is activated in mini-puberty and thereafter it is quiescent until puberty. We have shown that many girls with no clinical sign of puberty in the age group 1-6 yr. have a rather strong luteinizing hormone (LH) and follicle stimulating hormone (FSH) response to a gonadotropin releasing hormone (GnRH) test. However, stimulated LH and FSH values decreased in the age interval 1-6 yr and no LH/FSH values rose above 0.43. Serum estradiol has until recently not been detectable in pre-pubertal girls after the mini-puberty, but with new highly sensitive techniques estradiol may be measurable in most 1-6 yr. old girls. As both estradiol and inhibin B are produced in the granulosa cells we have examined how they associate in the age interval 1-6 yr.

Objective and Hypothesis: The objectives of the study were to investigate the associations between serum (se) estradiol, se inhibin B, GnRH stimulated LH (LH_{30}) and sex hormone binding proteins (SHBG) in the age group 1-6 yr.

Methods: Forty eight healthy girls aged 3.5 ± 0.2 yr. (range 0.8 – 5.9 yr.) were included in the study. All girls underwent a GnRH test. Estradiol concentrations were determined by on-line Turbo-Flow-liquid chromatography-tandem mass spectrometry, inhibin B by two-sided enzyme-linked immunosorbent assay, LH_{30} and SHBG by sandwich immunometry (Cobas 8000).

Results: Estradiol was measurable in samples from 40 girls. Medians and interquartile ranges were: se estradiol 6.66 (4.47;8.32) pmol /L, se inhibin B 13.00 (8.00;21.50) pg/ml, se LH_{30} 3.43 (2.39;5.19) IU/L, se SHBG 154 (114;177) nmol/L. Se estradiol ($r=-0.42$, $p<0.01$), se inhibin B ($r=-0.38$, $p<0.01$), se LH_{30} ($r=-0.59$, $p<0.001$) but not se SHBG ($r=0.07$, $p=0.66$) decreased significantly by age. Se estradiol associated positively with se inhibin B ($r=0.69$, $p<0.001$), while there were no associations between se estradiol and se LH_{30} and se SHBG, respectively. Neither did se inhibin B associate with se LH_{30} ($r=-0.10$, $p=0.51$).

Conclusion: By ultrasensitive technique circulating estradiol was measurable in most pre-pubertal girls in the age group 1-6 yr. Se estradiol and se inhibin B decreased in the age interval 1-6 yr. We observed a positive association between se estradiol and se inhibin B. This association did not seem to be LH driven.

P1-137

Brain MRI Findings in Girls with Central Precocious Puberty in Taiwan: one medical center experience

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Background: Central precocious puberty is defined by the onset of breast development before the age of 8 year in girls. Approximately 90% of girls have an idiopathic form without structural central nervous system (CNS) abnormality. It is controversial that all girl with central precocious puberty (CPP) should undergo brain magnetic resonance imaging (MRI) for intracranial pathology. To evaluate the outcome of brain MRI in girls with CPP and to identify the clinical and endocrine predictors of brain abnormalities.

Patients and Methods: This is a retrospective study conducted in Chang Gung Children's Hospital, between 1997 and 2017. 403 girls were consecutively diagnosed with CPP and 250 girls completed brain MRI study with detailed examination of hypothalamus and pituitary area. Patients with previous CNS insults, endocrinopathy or associated neuropsychiatric symptom/signs were excluded. Prevalence of brain abnormalities at MRI scan was measured. Demographic data including onset of puberty, initial pubertal status, height and weight, uterus and ovaries size measured by ultrasound, basal LH, FSH, Estradiol and the result of LHRH test was record.

Results: Brain MRI showed no alterations in 189 (75.6%), abnormalities of hypothalamic-pituitary area unrelated in CPP in 54(21.6%). Only one girl (0.4%) had pathological MRI findings

of hypothalamic hamartoma. 24.4% of girl with CPP has new diagnosed intracranial pathology and most of them are incidentalomas. The reported CNS alterations detected at diagnosis, except hamartoma, are as follows: pituitary microadenoma(12%), Cyst of pituitary pars intermedia(4.4%), Rathke's pouch cyst(2%), pituitary hypoplasia(1.6%), non-H-P arachnoid cysts(1.6%), pineal gland cyst(0.8%) and pituitary adenoma(0.4%). In our study, MRI follow-up was continued in 73.77% of cases, and did not show any progression or enlargement of the lesions. The lesions even disappeared in 19.67% of cases during follow-up. None of the girls with incidentaloma had other hormonal abnormality, nor did they underwent surgery. Girls with organic CPP had younger age of pubertal onset, early menarche, increased weight SDS, higher level of basal LH and estradiol, compared to girls with ICPP.

Conclusion: Only one in 250 (0.4%) of cases without prior symptom/signs of CNS lesions had true pathological MRI lesion (Hypothalamic hamartoma) that related to CPP. Among those with non-specific incidental findings of Brain MRI, none had progressively enlargement of lesion in 73.77% during 0.5-14 years follow-up. 19.67% had lesion resolution.

P1-138

Changes in body mass index in boys with central precocious puberty during and after gonadotropin-releasing hormone agonist treatment

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Background: Gonadotropin-releasing hormone agonist (GnRHa) treatment is widely used for central precocious puberty (CPP). Although some authors found increases in body mass index (BMI) in girls after GnRHa treatment, most studies reported no significant difference in BMI in girls during and after treatment. However, few studies have investigated changes in BMI in boys with CPP during and after GnRHa treatment. Hence, we aimed to evaluate the effects of GnRHa treatment on BMI in boys diagnosed with CPP.

Methods: This study included 75 boys who had been diagnosed with CPP at Ajou University Hospital between January, 2007 and December, 2016, and treated with leuprorelin acetate or triptorelin acetate every 4 weeks for at least 2 years. CPP was defined as the development of pubertal symptoms such as testicular volume $\geq 4\text{cc}$ before the age of 9 years, bone age advanced at least 1 year beyond chronological age, and a pubertal response to a GnRH stimulation test (peak luteinizing hormone response $\geq 5\text{ IU/L}$). The subjects were divided into three groups according to BMI: normal weight, overweight, and obese. We analyzed the BMI standard deviation score (SDS) in each group before treatment, after 1 and 2 years of treatment, at the end of treatment, and at 6 months of follow-up.

Results: Of the 75 boys, 37 were in the normal weight group, 21 were in the overweight group and 17 were in the obese group; 25 of the boys were followed up for at least 6 months after treatment (11 in the normal weight group, 9 in the overweight group, 5 in the obese group). All underwent brain MRI before treatment began, and 9 boys showed abnormal MRI findings. The mean BMI SDS for all boys at initiation of treatment was 1.0 ± 0.8 , and the BMI SDS in the normal weight, overweight, and obese group were 0.3 ± 0.4 , 1.3 ± 0.1 , and 1.9 ± 0.3 , respectively. Compared to the values before treatment, there were no significant differences in the BMI SDS in all patient groups after 1 or 2 years of treatment. Moreover, for the boys who were followed up for at least 6 months, none of the patient groups showed any significant differences in the BMI SDS before treatment, at the end of treatment, or at 6 months after the end of treatment.

Conclusion: The BMI SDS in boys with CPP did not significantly change during GnRHa treatment and after the end of treatment.

P1-139

Gonadal function of female patients with Noonan syndrome

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Background: Abnormalities in the hypothalamo-pituitary-gonadal axis have been reported in Noonan syndrome (NS) males but few data are available in female patients.

Objective: The aim of this retrospective study was to evaluate the gonadal function of female patients with NS and to look for genotype-phenotype correlations.

Patients and Methods: The study population included 19 girls/adolescents with a genetically confirmed diagnosis of NS and with available clinical (Tanner stages and age of first menstruations) and/or hormonal (serum gonadotropins, inhibin B, and anti-Müllerian hormone [AMH] levels) data on gonadal function.

Results: Twelve (63.2%) girls had entered puberty and the age at pubertal onset and at menarche were 12.0 and 15.0 years respectively, corresponding to a delay of 1.5 to 2 years compared with the general healthy population. Except two SOS1-patients with AMH values above the upper limit of normal, all AMH values were in the normal range through childhood and adolescence. NS girls had similar levels of inhibin B, transformed to age- and gender-

specific SDS using the published reference data, compared with the general population (mean SDS: 0.0; P = 0.94). Serum inhibin B levels SDS were significantly lower in NS with multiple lentigines (NSML)-PTPN11 patients compared with the general population and NS-PTPN11 patients (P = 0.01 for both); there was no other genotype-phenotype correlation.

Conclusions: These data suggest that NS females display normal albeit delayed onset at puberty and normal ovarian function.

P1-140

Methylation status of X inactivation-escape genes in controls and females with X chromosome rearrangements

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Context: X chromosome inactivation (XCI) is a process in which one of the two X chromosomes in a female is randomly inactivated in order to correct gene dosage between males and females. However, about 15% of genes escape from XCI (termed escapees), and 10% of genes are variably inactivated (variable genes). The mechanism of inactivation and escape remains to be revealed. The promoter regions of escapees are hypomethylated compared to those of the inactivated genes. The objects of this study are to confirm validity to predict escape genes by comparing methylation status of promoters between male and female controls and to reveal the influence on the methylation status of promoters of escapees in patients with X chromosome rearrangements.

Subjects: Four patients (XX) with X chromosome rearrangements and 11 female and 12 male controls.

Methods: We performed array-based methylation analysis on peripheral blood of patients and controls using Infinium MethylationEPIC BeadChip. We examined the methylation levels of the promoter regions located within 1 kb up and downstream of transcription start sites. In controls, we regarded the genes of which promoter regions showed equally hypomethylated in both sexes as "escapees".

The breakpoints of X chromosome rearrangements were determined by whole genome sequencing and Sanger sequencing.

Results: 51 genes were detected as escapee in controls. 74 % of them had previously reported as an escapee or a variable gene. One patient with 46,X,der(X)(pter→p22.13::p11.23→p11.23::p11.23→q22.1→q21.31::q22.2→q24::q23→q24::p22.11→p11.4::p22.1→p22.13::q22.1→q22.1::p22.12→pter) showed hypermethylation in five escapees. These genes could be partially inactivated. These genes were located in a duplicated region, however, most of the escapees at the duplicated region and all the escapees in regions with normal copy number remained hypomethylated in this patient. Three other patients did not have any hypermethylated escapees although the patients had duplications at Xp.

Discussion: Most escapees ascertained in this study were previously reported as escapees or variable genes. X chromosome rearrangements in a single patient affected the methylation levels of the promoters of five escapees. This finding suggest that structural abnormalities on X chromosome can affect the methylation levels of promoter regions in some escapees to result in inactivation.

Conclusion: We successfully determined escapees by comparing methylation status of promoters between male and female controls. Specific X chromosome rearrangements likely affect the methylation status of promoters of some escapees.

P1-141

Diagnostic Value of Anti-Müllerian Hormone Level in Adolescent Females with Polycystic Ovary Syndrome

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In adolescence, diagnosis of polycystic ovary syndrome (PCOS) is challenging because characteristics of normal puberty often overlap with signs and symptoms of PCOS. Anti-Müllerian hormone (AMH) is one of the important biomarkers suggested to confirm the diagnosis of PCOS and to manage the treatment process in adolescence. The aim of this study was to evaluate the diagnostic role of anti-müllerian hormone for PCOS in adolescent females, and to study its association to other diagnostic criteria of the disorder. A cross-sectional study was conducted on 30 PCOS patients aged 15-19 years (having all three of the Rotterdam Criteria: abnormal uterine bleeding indicative of chronic anovulation, clinical or laboratory hyperandrogenism, and a typical polycystic appearance of the ovaries on ultrasonographic examination), 30 high risk patients (incomplete PCOS with 2 of the 3 criteria), and 30 age and sex-matched controls. Exclusion criteria included chronic illness, other endocrine or genetic disorder causing hirsutism, patients taking medications that might potentially influence the biomedical assessments, e.g. oral contraceptive pills, metformin, anti-androgens.

Hirsutism was classified in terms of the distribution and degree of hair growth through Ferriman-Gallwey scale. The severity of acne was categorized as mild, moderate, or severe according to the classification system suggested by Luckey et al., 1997. Blood samples for hormonal assay were collected 5 days after menstruation. AMH, FSH, LH, prolactin, testosterone, estrogen, 17 hydroxy-progesterone. A single trans-vaginal ultrasound scan was performed at a random time (during the menstrual cycles) in the included married females. The number of follicles larger than 2.0 mm in each ovary was noted. The ovarian volume (cm^3) was calculated by the formula length (centimeters) \times width (centimeters) \times height (centimeters) \times 0.523. The results of these sonographic examinations were used to determine whether the woman fulfilled the criteria of having polycystic ovaries (PCO). The average ovarian volume was calculated summing the volumes of both ovaries and divided them by 2.

Mean serum AMH was 10.7 ± 5 ng/ml in PCOS patients, 22 ± 15 ng/ml in high risk group and 10 ± 5 ng/ml in controls. There was no statistically significant difference in serum AMH levels between PCOS patients and controls. During adolescence, especially at an early post-menarcheal age, the use of AMH levels as a diagnostic tool for PCOS is still controversial and more studies on this topic are needed.

P1-142

Disorders of sex development (DSD): Inconsistencies between clinical features and peripheral blood cultured karyotypes

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Sex differentiation and development are complex processes reflecting the precise spatiotemporal expression of specific genes and interactions among gene products. In some instances, peripheral blood karyotype diverges from anticipated findings based on phenotypic features. Ascertaining for chromosomal mosaicism aids the shared decision-making discussions with families and other health care providers. We have investigated for sex chromosome mosaicism in 13 patients by using fluorescence in-situ hybridization (FISH) on cells obtained from urine samples (5/13), cord blood (1/13), and uncultured peripheral blood (6/13). We compared cultured peripheral blood sample results to FISH results.

Twelve of thirteen patients had female phenotype. FISH analysis on uncultured peripheral blood cells identified 45,X cell line in 5 patients with normal 46,XX karyotype on cultured blood cells. In 2 patients, the percentage of mosaicism was higher from the FISH analysis on uncultured cells than cultured peripheral blood cells. One phenotypically female patient with 46,XY cell line on cultured peripheral blood cells had absence of SRY in 64.2% of uncultured urine cells indicating loss of Y chromosome or deletion of SRY gene among urine cells. Two phenotypic female patients with 46,XY karyotype had a 45,X cell line. One phenotypically male patient with 45,X karyotype on NIPT was found to have three other cell lines with the derivative Y chromosome markers in uncultured cord blood and urine cells. FISH testing resolved the sex chromosomal complement that was discrepant with the results of peripheral blood analysis.

Genetically abnormal cell lines dwindle and fail to survive in cell culture which contributes to underrepresentation of mosaicism in cultured cells. Therefore FISH studies on the uncultured cells are essential to establish a definitive diagnosis. Mosaicism is not always uniform throughout the body; somatic mutations can result in tissue specific mosaicism. These variations may contribute to the disparity in phenotype-genotype correlations among children with DSD and may impact clinical management. In our study, results obtained from urine samples appeared to better represent the percentage of mosaicism in gonadal tissues. Thus, this noninvasive method with direct genetic analysis of urinary epithelial cells may be helpful because urinary tract cells share similar embryonic origins with gonads.

Thyroid

P1-143

Biotine interference in a patient with non-clinic high thyroid hormone levels

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Introduction: Differential diagnosis of thyroid hormone resistance (beta) and TSHoma should be made in patients with high free thyroxine (f-T4) and free triiodothyronine (f-T3) and non-suppressed thyroid stimulating hormone (TSH) levels. The aim of this study was to present the results of etiological research in a patient with Down syndrome who was clinically euthyroid and had high levels of f-T4, f-T3, normal TSH levels.

Case: A 28-day-old male patient with Down syndrome was referred our hospital because of high f-T4 levels from another state hospital.

Background: It was learned that the patient was born 3270 g, operated for pediatric surgery for hirschsprung disease and used biotin at a dose of 10 mg / day due to biotinidase deficiency.

Family History: Parents had no known thyroid dysfunction.

Physical Examination: Weight 4020 gr (-0.68 SDS), Length 52 cm (-0.55 SDS), Head circumference: 38 cm (0.07 SDS), Pulse: 130 / min, Blood pressure: 90/50 mmHg, the anterior fontanel was 1.5x1 cm, the thyroid was non-palpable, the other system examinations were normal, other than the Down syndrome stigmatics.

Laboratory: fT3: 14.9 ng / dl (2.5-4.4), fT4: 4.08 ng / dl (0.54-1.24), TSH: 2.65 mU / L (0.34-5.6), After 1 week of repeated tests in the same laboratory; fT3: 14.3 ng / dl (2.5-4.4), fT4: 3.69 ng / dl (0.54-1.24), TSH: 2.88 mU / L (0.34-5.6).

Clinical Follow-up: As the patient was clinically euthyroid and had a history of biotin use, the method of TFT was investigated with biotin interference. The patient's sT3 and sT4 tests were found to be studied in an immunoassay system (Dxi, Beckman Coulter Inc., USA) using streptavidin-biotin and interfering with it. There was no interference in the same tests on a different immunassay platform (Architect 2000, Abbott Lab., USA) which did not use this pairing methodically. fT3: 3.64 pg / ml (1.5-6.4) fT4: 1.17 ng / ml (0.48-2.34) TSH: 2.53 uIU / ml (0.62-8) was normal.

Conclusion: Biotin-streptavidin interaction is the most potent non-covalent interaction in nature and is frequently used in immunoassay measurements. The direction and magnitude of the biotin interferants may vary depending on the immunoassay platform and test run. In particular, the use of high-dose biotin may result in erroneous results depending on the principle of the test (competing or sandwich). It is an appropriate approach to repeat the analyzes in alternative immunassay platforms in cases where interference is suspected.

P1-144

Investigation of Iodine Deficiency in the North of Siberia

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Introduction: Siberia traditionally belonged to iodine-deficient regions. Cessation of iodine prevention in the 1990-s promoted the increase of iodine deficiency disorders (IDD) in Siberia. For iodine prophylaxis now is used iodized salt, and iodine preparations.

The Aim: To estimate the iodine deficiency, the prevalence of IDD and the effectiveness of iodine prophylaxis in the North of Krasnoyarsk territory.

Methods: We performed a complex investigation of IDD in the North of Krasnoyarsk territory: in the Igarsky, Turukhansky, and Yenisseiskiy regions. 6180 schoolchildren participated in this survey. In accordance with the WHO recommendations, the assessment included clinical examination, measurement of weight and height; thyroid palpation and ultrasound scan; plasma TSH, T₄ and thyroglobulin (TG); urine samples collected in the field and processed for iodine using conventional technique; the analysis of the results of neonatal TSH - screening.

Results: Our epidemiological studies of IDD revealed a moderate iodine deficiency in the northern regions the Krasnoyarsk territory. The median urinary iodine in prepubertal children varied from 30 to 42 mcg/l. The goiter prevalence varied from 42.5% to 58.4% according to thyroid palpation and ultrasound scan in prepubertal children. The median serum TG was from 14.7 to 31 mcg/l and also corresponded to moderate iodine deficiency. Analysis of neonatal TSH screening in the Krasnoyarsk region has shown that, in whole, the frequency of neonates with TSH >5 µU/ml was 11.8% (in 2000 was 23.9%). The IDD monitoring showed that median urinary iodine in prepubertal schoolchildren increased up to 115 mcg/l. Thus, IDD prevention in these regions was effective.

Conclusions: Our investigations show that in the North of Krasnoyarsk territory there is a serious natural iodine deficiency influencing the health of the population and demanding continuous adequate iodine prevention to prevent cognitive and psychomotor outcomes.

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P1-145**The investigation of genetic etiology in familial cases with congenital hypothyroidism**

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Background: Congenital hypothyroidism(CH) is the most common neonatal endocrinological disorder in the world. Although most of the CH is sporadic, some genetic defects are responsible from the etiology. The aim of this study was to determine the genetic and etiological factors of CH.

Methods: 49 patients(female; n=24), from 24 families were included in the study. The data, collected retrospectively, consisted of medical history, physical examination, clinical findings, thyroid hormone levels and etiological tests. Gene panel consisting of 19 genes(PAX8, NKX2-1, NKX2-5, FOXE1, TSHR, SLC5A5, SLC26A4, TG, TPO, DUOX2, DUOXA2, IYD, SLC26A7, DUOX1-ZNF607, SLC6A4, GLIS3, TSHB, THRA) that may cause CH was performed. Pathogenicity of the novel nonsynonymous mutations were analysed via *in silico* prediction programs.

Results: Sixteen families had consanguineous marriages and 12 families had a history of hypothyroidism. Twenty patients were diagnosed with neonatal screening programme and 2 patients with hyperbilirubinemia, 5 patients were diagnosed during hospitalization in neonatal intensive care unit and 22 patients were diagnosed during the routine control. The mean age at presentation (mean±SD) was 1.3±2.1 years (median:0.2;range0.03-8.8). The mean TSH level at presentation was 152.3±207.9mIU/ml (median:51.8;range4.2-820), and the level of fT4 was 8.8±5.9 pmol/L(median:9.4;range0.04-19.7). All patients underwent ultrasonography and one patient had thyroid agenesis. Scintigraphy was performed to 23 patients and thyroid agenesis and thyroid hyperplasia were detected in two patients. Perchlorate discharge test was performed on 21 patients and two of them could not be evaluated due to errors in processing. Four patients had normal results, 9 patients had partial dyshormogenesis and 6 patients had complete dyshormogenesis. Genetic analysis revealed that four families with consanguineous marriages (4/24,16.7%) had mutations in 3 different genes. Two families were followed because of complete dyshormogenesis and two families were followed because of partial dyshormogenesis. Family I had a homozygous c.1349G>A(p.R450H) mutation in the TSHR gene. Second family had a homozygous c.1477G>A(p.G493S) mutation in the TPO gene. Third family had a homozygous missense p.R540X mutation in the TPO gene. Family IV had a homozygous novel c.280G>A(p.G94R) mutation in the SLC26A7 gene.

Conclusion: In our study, the overall mutation rate was 16.7%. Genetic etiologies may differ in patients with dyshormonogenesis. A novel mutation was shown in the SLC26A7 gene in a family with partial dyshormogenesis. Genetic analysis can be used to clarify the

etiology, to be informed about prognosis and to provide genetic counseling especially in familial cases. It has been suggested that a greater number of related genes should be screened for the recognition of genetic causes that may cause of CH.

P1-146**Is there any correlation between thyroid function test on first day of admission in critically ill children and disease severity or outcome?**

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Sick euthyroid syndrome (SES) is the most common endocrine disorder in critically ill patients. It has been shown that the decrease in T4 levels correlates with disease severity and prognosis. Whether SES is a compensatory response to the disease course or needs to be treated is not known yet.

To our knowledge, there are only a few studies on critically ill infants and children investigating the correlation between thyroid function and disease severity as well as its outcome. Therefore, this study aimed to investigate thyroid hormone levels in critically ill patients. In this study, thyroid function tests including thyroid stimulating hormone (TSH), total T3 (TT3), free T3 (FT3), total T4(TT4), free T4 (FT4), and reverse T3 (rT3) were measured in 35 critically ill children admitted to intensive care unit (ICU) on days 1. Disease severity was evaluated using pediatric logistic organ dysfunction score (PELOD). Then the patients were divided into groups of survivors and non-survivors and the results were compared between these two groups accordingly. Thirty-five patients, including 19 (54.3%) female and 16 (45.7%) male, with the mean age of 2 years (SD: 3.8 years, range: 4 months- 15 years) had entered the study based on the inclusion criteria. 25 (71.6%) patients were transferred from PICU to other wards and 10 (28.4%) patients died. Age and sex were not statistically different in survivors and non-survivors ($P > 0.05$). It was revealed that there was a significant reduction in mean TT3 levels in non-survivors compared to survivors on the first day of admission ($P = 0.007$).

Conclusions: Thyroid function assessment, especially TT3 on the first day of admission, along with PELOD score, might be helpful in predicting disease outcome and patient's survival.

P1-147**Intrathyroidal ectopia of thymus in children: frequency, ultrasound, evolution**

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Objectives: to study the frequency, ultrasound characteristics and the evolution of intrathyroidal ectopia of thymus(IET) in children.

Materials and Methods: as part of an epidemiological study (2014-2017), an assessment consists of incidence of IET in pre-puberty children, which using ultrasound of 1164 patients (604 girls, 560 boys). As part of a clinical study (2014-2019), the ultrasound characteristics and the evolution of IET in pre-puberty children were counted. The follow-up period ranged 0.75-2.17 years, with an average of 1.57 ± 0.44 years. Ultrasound of the thyroid gland(TG) was made on the GE Healthcare LOGIQ P6 (USA) apparatus using a 9-15 MHz linear sensor.

Results: According to the results of an epidemiological study, focal thyroid pathology was diagnosed in 1.5% of patients(17/1164, 11 girls, 6 boys), which 1.3% had an IET(15/1164, p=0.0000, 10 girls, 5 boys, p=0.09), in 0.1%(1/1164, 1 girl) the node goiter, in 0.1%(1/1164, 1 boy) the diffuse nodular goiter. Age of patients with IET was 6.88 ± 0.36 years. All cases, ultrasound of IET was similar with the characteristics of the correctly located thymus and was a focal formation localized inside the TG equally often in both (8/7, p=0.41) lobes closer to the lower departments, fusiform, with a wavy contour, without a capsule, hypoechoic structure with multiple small hyperechogenic inclusions, avascular, with a diameter 0.94 ± 0.26 cm. By diameter (0.9 ± 0.28 cm VS 1 ± 0.23 cm, p=0.5), location on the left (girl / boys: 5/3, p=0.26) and in the right lobes (girl / boys: 5/2, p=0.18) thymus ectopated into the TG tissue in children are equal.

The follow-up of patients showed that IET persisted at the age of 7 years - in 73% (11/15) of cases, at the age of 8 years - in 7% (1/15) of cases (one boy from the group of frequently ill children). In this patient, thymus tissue ectopated into the TG decreased (by 1.8 times), but didn't completely disappear, while the initial diameter of focal formation (0.77 cm vs 0.95 ± 0.26 cm, p=0.53), age at the time of the last TG ultrasound (8.3 years vs 8.46 ± 0.52 years, p=0.65), observation period (2 vs 1.54 ± 0.44 years, p=0.17) didn't differ from those patients who had regressed IET.

Conclusions: In the structure of focal pathology of TG in children of pre-school age, IET takes the leading place. In the beginning of puberty period, IET can regress. Sonographic characteristics knowledge of IET allows ultrasound to optimize the management tactics of this children group.

P1-148**Activating mutation M453V in receptor TSHR as a cause familial hyperthyroidism**

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The most common hyperthyroidism in children is Graves' disease. The other rare cause of hyperthyroidism is activating mutation in receptor TSHR in thyroid gland.

We would like to introduce a case of familial hyperthyroidism with a novel mutation M453V in the TSHR in three members

Actually 11-year-old boy is a patient in outpatient clinic for first days after birth. During gestation his mother was treated with thyreostatic drugs because of Graves's disease. In newborn we diagnosed hypothyroidism and started therapy with l-thyroxin. Because of rapid normalisation of TSH, low levels of his antithyroid antibodies and normal thyroid gland by ultrasonography we finished his therapy with l-thyroxin when he was 6 months. When he was 3 years, he lost his body mass, he had tachycardia and advanced bone age (7 years). In laboratory labs TSH was decreased, elevated free thyroid hormones, with normal level of anti-thyroid antibodies. In ultrasonography thyroid tissue was with excessive flow. We diagnosed hyperthyroidism and we started treatment with taking methamizol, beta-blocker. We had not observed any side effects connected with the anti-thyroid therapy. The tests of stopped that therapy were ineffective and now we make a plan the radical therapy.

His actually 40-yrs-old mother was diagnosed Graves' disease when she was 6 years. She started the typical therapy of hyperthyroidism. She had positive family history with Graves' disease (her father and her 2 siblings). Because of ineffective drug therapy, she had strumectomy at 12-yrs aged. Because of recurrence of hyperthyroidism and presenting enlarged multinodular goitre pressing trachea in ultrasonography, she had the second strumectomy, when she was 30 years old. After surgery she had radioiodine therapy to eliminate thyroid tissue. In effect now she has hypothyroidism and she is administered with l-thyroxin.

Her younger son, who was born after second strumectomy, was admitted to our outpatient clinic when he was 6 years because of hyperthyroidism and we started appropriate therapy.

In order to find genetic basic of familial hyperthyroidism in mother and her children we identified a novel activating mutation M453V in receptor TSHR(heterozygous c.1357A>G), which initiates excessive production thyroid hormones and hyperthyroidism.

To summary, in case of familial hyperthyroidism it is worth to find and identify mutation in genes in receptor TSHR, which may determinate risk assessment of hyperthyroidism and may use earlier appropriate therapy. The patients with activating mutation in receptor TSHR often need radical therapy, because long term therapy with thyreostatic drugs is ineffective.

P1-149**Central hypothyroidism with pituitary enlargement and no gene alterations**

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Introduction: Central hypothyroidism is due to a deficiency of TRH/TSH.

Patient and Methods, Results: A 9 year old boy (07 Aug. 20) was referred for proportionate short stature (-2.7 SD). He complained of fatigue and had mild peripheral edema.

His baseline T4 was 2.9 ug/dL (ref. 4.50-12.50 ug/dL) and TSH 0.04 uIU/ml (0.400-4.00). The TRH test showed low TSH <0.004 Ulu/ML (ref. 0.400-4.00) and low T4 2.70 (ref. 4.50-12.50 ug/dL). Prolactin concentrations were within normal range. MRI of sella showed enlargement ("tumor") which was significantly decreased after one year of treatment with sodium L thyroxine. Tests of pituitary reserve of growth hormone yielded normal growth hormone concentrations. Ultrasound of the thyroid showed homogenous thyroid with moderately decreased.

Genetic Analysis: The most likely genes involved in central hypothyroidism were sequenced: *TSHB*, *IGSF1* and *TRHR* and no gene alterations were found. *PROPI* mutations were not tested as the child did not have combined pituitary hormone deficits. Mutations in *TBL1X* and *IRS4* are going to be analyzed in the near future.

Conclusion: We present a child with central hypothyroidism who manifested an enlargement of the pituitary gland which was almost totally removed by sodium L thyroxine treatment after one year.

Key Words: Macedonia, Central hypothyroidism, genetics, pituitary enlargement.

P1-150**Acquired Von Willebrand's syndrome caused by primary hypothyroidism in a 5-year-old girl**

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Background: Acquired Von Willebrand's syndrome (aVWS) associated with hypothyroidism is rare in children and more often diagnosed during the peripubertal period in the context of Hashimoto's thyroiditis.

Case Presentation: A 5-year-old girl was referred to the paediatric haematology unit for rectal bleeding, anaemia, and prolonged activated partial thromboplastin time. Her developmental and learning skills were normal. The physical examination revealed severe short stature (height SDS: -3.6) with overweight (body mass index SDS: 1.8) and clinical sign of hypothyroidism. Laboratory investigation revealed aVWS type 1 associated with severe primary hypothyroidism. Anti-thyroid antibodies were negative and thyroid ultrasound found thyroid hypoplasia in favour of congenital hypothyroidism. Restoration of euthyroidism was associated with increased growth velocity and normalization of coagulation parameters. Conclusion: This report highlights the importance to exclude an underlying pathology (including hypothyroidism) in children with suspected VWS, even in young age.

Key words: Acquired Von Willebrand's syndrome; Hypothyroidism; Children.

P1-151**Iodine Status in Newborns and Mothers in Georgia**

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Background and Aims: For years Georgia belonged to a iodine deficiency endemic region, though as a result of a long-term actions aimed at improving the iodine status the country today is a non-iodine deficient region. For this reason it was decided to study present iodine status of newborns and their mothers leaving in the capital of Georgia, which is no longer non-iodine region.

Materials and Methods: In total 87 newborns born to euthyroid mothers (TSH – 2.3.±0.7 IU/L) with insufficient (low normal) urine iodine level comprised group (Gr.) 1; 51 newborns born to euthyroid mothers with sufficient urine iodine levels were included into Gr. 2; These investigations were carried out: thyroid ultrasound, blood TSH level, iodine concentration in urine and breast milk in mothers; Besides, In newborns - urine iodine level (with ammonium persulfate method) Iodine concentration in meconium (measured with Scholz kinetic method). Newborn screening for hypothyroidism data was considered (TSH levels were measured on 3-4 post-delivery).

Results: Results achieved show, that in Gr.1 fetal chronic hypoxia is evidently more frequent (18,3 %), than in Gr.2 (3%), ($p<0,05$), late meconium pass (Gr. 1 -32%, Gr. 2 -1%), TSH (Gr.1 – 4.4±1.4 IU/L; Gr.2 – 2.8 ±0.39 IU/L) were statistically higher in Gr.1 newborns, than in Gr.2 ones.

Urine iodine level: Gr. 1 - 9.7 ±0.5 mkg/dl, Gr.2 -11.3 mkg/dl, which was statistically higher in Gr.2 than in Gr.1. Ioduria mediana in Gr. 1 mothers was 13.3±3.1 mkg/dl, while in Gr.2 it was 15,4±1.8 mkg/dl. Iodine concentration in breast milk was statistically lower in Gr.1 (7±0.9 mkg/dl), than in Gr.2 (8,6±0,1 mkg/dl). The results indicate that breast milk iodine mediana is lower, than that in urine.

Iodine concentration in newborns' meconium was statistically lower in Gr.1 babies, than in Gr.2 ones (80±2,3 ng/g vs. 97,5±1,8ng/g), ($p<0,05$). It was found in those, whose iodine level in meconium and urine was low, relatively high TSH levels were observed.

Conclusion: Meconium iodine level in new directly correlates to breast milk iodine level, and newborns' blood TSH level. Iodine concentration in meconium reflects fetal iodine metabolism integral status.

P1-152**Thyroid function following Hemithyroidectomy in a Pediatric Cohort**

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Background: Studies about thyroid function following hemithyroidectomy are scarce in the literature and no studies include pediatric population.

Objective: To describe thyroid function in pediatric patients who underwent a hemithyroidectomy.

Design: Retrospective cohort study.

Patients and Methods: Among the 38 patients who underwent hemithyroidectomy from 2006 to 2018, a total of 24 patients with available data who were followed up for more than a year and who were free of treatment at consultation were included in the analysis.

All patients were analyzed for age, sex, surgical indication and final pathologic analysis. Thyroid function (TSH, free T4 (fT4) and antithyroid antibodies (Ab)) were measured preoperative (P1) and postoperative (1-3 (P2) and 12-36 (P3) months). Paired Anova test was performed to evaluate TSH and fT4 levels ($p < .05$).

Results: Median age at surgery was 13.4 years (r:3.3-17.7), 21 patients were female (87%). Pathologic analysis showed 10 follicular adenomas, 12 nodular hyperplasia and 2 suppurative thyroiditis. 2/24 showed positive thyroid antibodies. At P1 all the patients were euthyroid except 2 who were hyperthyroid and were excluded. 22 patients were evaluated at P2: 3 patients with a TSH > 10 mIU/L (overt hypothyroidism) and 7 with TSH 5-10 mIU/L were assumed as subclinical hypothyroidism with different criteria and initiated replacement with LT4 (only 1 was reevaluated 6 years after showing a normal thyroid function). The remaining 12 patients who were not treated (final cohort) were reevaluated at a minimum of 12 months after surgery (P3). Median TSH and fT4 at P1 were 1.2 mIU/L (r:0.8-2.2) and 1.2 ng/dl (r: 1-1.9), respectively. TSH at P2 showed a significant elevation when compared to TSH at P1 ($p < .05$). TSH at P3 showed a significant decline when compared to TSH at P2 ($p < .05$). TSH at P3 showed no difference to TSH at P1. fT4 was normal at P1, P2 and P3 showing no differences between them.

Conclusions: Thyroid function in this cohort of 12 pediatric patients who were not treated after hemithyroidectomy had transient thyroid function changes characterized by a significant elevation of TSH at P2 and a significant decline at P3 – reaching similar levels to that observed at P1 - with a stable fT4 suggesting an adaptive response. Even when our cohort is too small, our results could suggest that the replacement with LT4 for subclinical hypothyroidism should be determined in a more cautious manner considering that the elevation of TSH < 10 mIU/l with normal fT4 can spontaneously normalize in further controls.

P1-153**Homozygous c.2422delT hTPO mutation in three patients with congenital hypothyroidism followed over 20 years**

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The homozygous deletion c.2422delT in the carboxyl-terminal coding region of the hTPO gene results in a frameshift mutation and leads to an early stop codon in exon 14 of the gene (p.Cys808AlafsX24). Combination with double heterozygous DUOX2 mutations was also reported. We present the data on the clinical course of CH in three patients with permanent congenital hypothyroidism (CH) harboring one and the same mutation. Pat1 was followed 29 yrs; after an uneventful pregnancy (no consanguinity) and vaginal delivery she was diagnosed at 38 d by clinical signs (severe prolonged jaundice due to indirect hyperbilirubinemia, constipation, feeding difficulties, edema, delayed bone age, hoarse voice) before the screening introduction. She was started on L-thyroxine (25 mcg/d) on d36 (pretreatment TSH > 43 mU/l, fT4 1.2 pmol/l), adjustments were performed, but TSH was often above 5 mU/l. The development milestones were normal, she had excellent marks during school attention, graduated and is working. Her younger brother was diagnosed at d10 (TSH 368 mU/l, fT4 0.7 pmol/l), L-T4 was given initially at a dosage of 25 mcg/d (10 days) and 50 mcg/d thereafter. Normal motoric and intellectual development were noticed, an eutopic thyroid as well. Pat3 was picked up by TSH screening (NTSH 238 mU/l d3), the high CH suspicion was confirmed on d22 (TSH > 900 mU/l, T4 < 20 nmol/l, Tg 490 ng/ml) and 50 mcg/d L-T4 were given. His thyroid volume increases with elevation of the TSH (several times) and multinodular goiter developed bilaterally, therefore the thyroid was extirpated at 19 yrs. After informed consent molecular analysis of the hTPO gene (Sanger sequencing) was performed in all three patients and the same homozygous previously described mutation c.2422delT could be detected. In conclusion: follow up data combined with molecular genetics could help in personalizing the treatment (no re evaluation needed) and facilitate the possibilities for genetic consultation. Thyroid US (at diagnosis and during follow up), in CH patients with eutopic glands combined with frequent hormonal controls are highly advisable.

P1-154**Association of Hashimoto's Thyroiditis with Antistreptolysin O titer**

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Background: Hashimoto's Thyroiditis (HT) is a relatively common autoimmune disorder that involves both cellular and humoral immunity, the latter characterized by the presence of antithyroid antibodies. Nevertheless, despite the large number of relevant studies, the underlying pathogenetic mechanisms still remain unclear; evidence and indications pointing to both genetic and environmental components. Genetic studies have uncovered molecular associations that include immunoregulatory and thyroid specific genes. Possible environmental triggers of the autoimmune process have included the hygienic conditions, selenium and vitamin D deficiency, drugs, stressors, smoking, alcohol, toxins and infections such as HHV-6, Yersinia and the Hepatitis C virus. Streptococcal infections are known triggers of autoimmune processes such as rheumatic fever, glomerulonephritis and CNS autoimmune disorders.

Objective: The objective of this pilot study was to examine whether an association between HT, developing during childhood and adolescence, and Streptococcal infections exists.

Subject and Methods: The study group included a total of 106 children (73 females and 33 males), aged 9.9±2.9 years, initially examined for various reasons in a pediatric endocrinology setting (idiopathic short stature, early puberty, premature adrenarche, slightly elevated TSH with normal thyroid hormones in routine screening or a family history of HT). Antithyroid antibodies (antiTPO and antiTg) and Antistreptolysin O (ASO) titer, a marker of Streptococcal infection, were determined. For ASO, a titer >200 IU was characterized as positive. Appropriate statistical analysis was applied.

Results: In the group of children with a positive ASO titer, presence of positive antithyroid antibodies was observed in a significantly higher percentage of children (in 68.6 %) compared to those with a negative ASO titer (in 31.40%, p = 0.001). With respect to gender, the difference in positive antithyroid antibodies was significant only in females (p=0.002 in girls and 0.282 in boys). ASO titer was significantly increased in the positive with respect to the negative antithyroid antibodies group (p<0.001). ASO positivity was not related to age nor affected by season (cold or warm months) of specimen's collection.

Conclusions: We attempted to examine whether the range of autoimmune disorders associated with streptococcal infections includes Hashimoto's Thyroiditis. A significant association of ASO positivity with the presence of antithyroid antibodies was revealed in females. Our observational data obtained from a relatively small number of children and adolescents cannot reveal whether this association is causal or the result of a common underlying immuno-regulatory disorder.

P1-155**Congenital hypothyroidism newborn profile after a lower TSH cutoff for neonatal screening in Southern Brazil**

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Introduction: The ideal TSH filter value (TSHf) in the neonatal screening tests for Congenital hypothyroidism (CH) is worldwide controversial. Local cutoff point of TSHf was 9.0 mIU/L until recently.

Objective: To evaluate the clinical and laboratory characteristics of newborns with CH (confirmatory serum TSH > 10 mIU/L) after a lower TSH cutoff.

Methods: Cross-sectional study using data from Neonatal Screening Reference Center of State Rio Grande do Sul, 2018. All cases with TSHf ≥ 6.0 mIU/L were evaluated. A second filter test was performed if the first one (TSH1) was between 6 and 9.0 mIU/L. Newborns with a second TSH filter (TSH2) above 6 mIU/L were called up for confirmatory tests and clinical evaluation.

Results: Of the 106,594 screening tests, 244 (0.22%) resulted in TSHf ≥ 6.0 mIU/L. Patients with TSHf1 > 9.0 mIU/L [58 (24%)], were called up for immediate confirmatory tests; patients with TSHf1 6-9.0 mIU/L, [186 (76%)], were submitted to a second filter test (TSHf2). Of these, 153 (82.25%) were discharged after TSHf2 < 6.0 mIU/L. Patients with TSHf2 > 6 mIU/L (21 cases) were referred for consultation. Twelve cases did not perform the second test and were not included. The incidence of altered tests was 7: 10,000 (95% CI: 6-9). The cases were classified by group (G) was: G1: TSHf1 and TSHf2 > 6.0 and < 9.0 mIU/L [11 (13.9%)]; G2: TSHf1 > 6.0 and < 9.0 mIU/L and TSHf2 > 9.0 mIU/L [10 (12.7%)]; G3: TSHf1 > 9.0 mIU/L [58 (73.4%)]. The cases of CH (serum TSH > 10 mIU/L) were 9 (81.8%), 10 (100%), 33 (58.9%) in G1, G2 and G3 respectively. The prevalence of CH was 1:2000. Consanguinity, gestational thyroid disease and presence of congenital malformations were more prevalent in G1, Drug addiction and genetic syndromes were more present in G2.

Conclusion: The new cutoff point identified about 19 patients/year. This cases would no longer be diagnosed early if the previously established cutoff point was sustained. Despite the small number of patients studied and a short period of evaluation, these results support the new cutoff proposal. Furthermore, the presence of consanguinity, malformations and/or syndromes in the groups with TSH filter of lower cutoff points draws attention to the possibility of a diagnosis of CH.

Adrenals and HPA Axis

P1-156

Prospective, open-label, long-term follow-up of neonates and young children with Adrenal insufficiency treated with Hydrocortisone Granules

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Introduction: Children with congenital adrenal hyperplasia (CAH) and adrenal insufficiency (AI) rely on lifelong hormone replacement with hydrocortisone (HC). Alkindi® is the first HC licensed for children from birth to 18 years with AI, available in small doses of 0.5, 1, 2 and 5mg required for the needs of neonates, infants and children.

Objectives: Primary: long-term safety of Alkindi®; Secondary: long-term disease control in children aged 0-6 years.

Methods: Of the 24 patients who completed the initial Phase 3 trial, 18 patients, aged 0-5 years, were enrolled in this long-term study (CAH, n=17; hypopituitarism, n=1). Median ages at entry were 3.6 years in cohort 1 (2- < 6 years in the initial trial, n=9), 2 years in cohort 2 (1 month- < 2 years in the initial trial, n=6) and 46 days in cohort 3 (<28 days in the initial trial, n=3). Ten subjects were male, all were white (Caucasian). Children were observed by two visits every month, followed up by 3 monthly visits thereafter. Therapy was controlled by routinely taken 17-OHP saliva sampling every three months starting from 3-6 months of age.

Results: Children were observed over >2 years (median 795 days (1-872 days)). Six, mainly older children, withdrew their consent due to personal reasons. All other children were compliant with treatment. Hydrocortisone granules (Alkindi®) were prescribed every 8 hours with a mean daily dose per BSA between 10.98 – 12.85 mg/m² in cohort 1, 9.17 – 10.64 mg/m² in cohort 2 and 10.46 – 17.52 mg/m² in cohort 3. All but one patient with panhypopituitarism received additional fludrocortisone therapy.

Safety: No cases of adrenal crisis and no AEs of choking. A total of 193 treatment-emergent adverse events (TEAEs) were reported by 14 subjects (77.8%) with the primary diagnosis being fever and viral upper respiratory tract infection. No deaths, severe TEAEs, TEAEs leading to withdrawal from the study and no TEAEs with a suspected causal relationship to Alkindi®. Nine serious adverse events (SAEs) were reported in three patients (gastroenteritis, vomiting, urinary tract infection, erysipelas), all of them considered not related to Alkindi®.

Efficacy: Standard deviation scores for height and weight showed no trends for accelerated or reduced growth.

Conclusions: During >2-year follow up of children aged 0-7 years, no AEs related to Alkindi® treatment and no adrenal crisis occurred. All children grew along their expected percentiles. Mean daily HC-dose controlled by routine saliva sampling was at the lower recommended dose-range.

P1-157

Influence of salt supplementation on drug therapy in children with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency aged 0-3 years: Update on a retrospective multicentre analysis using the I-CAH registry

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Introduction: Classic congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency results in impaired synthesis of gluco- and often also of mineralocorticoids. Early treatment with glucocorticoids and mineralocorticoids prevents life-threatening crises. In some centres, additional salt is prescribed in the first year. However, until now the use of salt is controversial and not proved to result in better outcome in studies.

Objectives: Primary aim: to evaluate the effect of additional salt supplementation on the fludrocortisone (FC) dosage in young children (0 – 3 yrs). Secondary aim: to evaluate effect of additional salt supplementation on hydrocortisone (HC) dosage, height and blood pressure

Methods: Retrospective analysis of patients born after 2000. Longitudinal data of the I-CAH (International congenital adrenal hyperplasia)-registry were extracted and divided in a salt treated (ST) (at least between two visits between 46 and 136 days of life) and a non-salt treated (NST) group. HC and FC dosage, weight,

height and blood pressure were analysed at birth, 3, 6, 9, 12, 18, 24, 30, 36 month of age.

Results: A total of 2672 visits of 355 patients born after year 2000 and treated in 23 centres from 13 countries were analysed (actual assigned sex male – n=155 and female – n=200) with 114 patients (32.1%) in the ST group. Mean dose of FC was reduced in the ST group from birth until 18 months compared to the NST group. Dose of FC at 3 month of age: ST 362.98+/-220.91 µg/m² BSA vs. NST 386.46+/-186.72 µg/m² BSA. Mean dose of HC was not different between the groups. There were no clear differences in body weight and body length between the groups at the different time points. Although, in the ST group height and weight development were closer to the normal population and the systolic blood pressure was slightly lower.

Conclusion: Salt supplementation in newborns and infants suffering from classic CAH might reduce FC-dose and therefore reduce side effects on blood pressure in these children. Further longitudinal follow up is necessary to examine the effect on long-term parameters.

P1-158

Influence of Internal Standards Choice on Quantification of 17α-hydroxyprogesterone (17OHP) Using Mass Spectrometric Based Methods

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Objective: This project aims to evaluate the effect of two isotopically labelled internal standards on the quantification of 17OHP by liquid chromatography-tandem mass spectrometry (LC-MS/MS) and gas chromatography-tandem mass spectrometry (GC-MS/MS) as an orthogonal technique.

Methods: Three LC-MS/MS and one GC-MS/MS laboratories, spanning four countries worldwide, who routinely measure serum 17OHP, compared two internal standards as part of their patient runs. The only change to the respective laboratory standard operating procedure was the substitution of their internal standard (if different to in-house method) with: 1) IsoSciences carbon-13 labelled 17OHP-[2,3,4-¹³C₃]; and 2) IsoSciences deuterated 17OHP-[2,2,4,6,6,21,21-D₈]. Statistical interpretation of the

data is based on the slope from the Passing Bablok regression, difference from the Bland Altman plots and the Student two tailed paired t-test, with confidence intervals (CI) of 95% and level of significance p<0.05 applied.

Results: The three LC-MS/MS and one GC-MS/MS laboratories successfully evaluated the two internal standards against altogether 232 patient samples. Analysis of the ¹³C- and D-labelled internal standard results from the individual laboratories, along with the combined all laboratory data, demonstrated agreement: the Passing-Bablok regression slope to include one in the CI; and Bland Altman difference to include zero in the CI. The all laboratory data t-test demonstrated a p>0.05

Conclusions: Overall, the comparison between the results of ¹³C- and D-labelled internal standards for 17OHP showed not influence by the internal standard used.

P1-159

Characteristics of puberty, pubertal height gain and final height in children with classical 21 hydroxylase deficiency

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Context: There is a limited data from large cohorts regarding pubertal characteristics of children with classical 21-hydroxylase deficiency (21OHD).

Objective: To explore the timing and tempo of puberty, and pubertal height gain (PHG) in children with 21OHD-CAH.

Design: A multicenter observational, retrospective, longitudinal analysis.

Patients: Data from 283 patients (876 visit measurements) with classical 21OHD (195 salt-wasting(SW) and 88 simple-virilising(SV)) were analysed.

Main Outcome Measures: Ages of attainment of Tanner stages, bone maturation, height gain, final height(FH), midparental height(MPH) were collected. Puberty modifying therapies(PMTs) such as gonadotropin releasing hormone analog(GnRHa), aromatase inhibitors(AI) and cyproterone acetate(CPA) were recorded.

Results: 152 of 283 patients were pubertal/postpubertal (85F, 67M). PMTs (GnRHa, AI and CPA) had been used in 18.2, 1.3 and 7.0% in females and, 27.4, 10.5 and 10.5% in males, respectively due to early puberty. In girls, the median age of attainment(MAA) of breast stage 2(B2) was 8.9(IQR:7.8-10.0)years. In those, who did not receive PMT, MAA of B3 through B5 were 11.1, 12.4, and 14.2years, respectively, and median age of menarche was 13.2years. MAA of pubic hair stage 2(P2) was 8.4years. In girls

with longitudinal data from B2 to final height and no PMTs, duration from B2 to menarche was 3.4years, B2 to B5 was 3.6years, height gain from B2 to menarche and B2 to final height was 13.9 and 17.5cm, respectively. In girls who received PMTs, these figures were 5.5years, 6.4years, 21.7cm and 24.1cm, respectively. In boys, the MAA of G2 through G5 were 8.8, 12.7, 13.7, and 15.1years and P2 was 8.2years. In boys with longitudinal data from G2 to final height and no PMTs, median duration from G2 to G5 was 4.1years, height gain from G2 to G5 and G2 to final height was 21.0cm and 28.1cm, respectively. In boys who received PMTs, these figures were 7.5years, 29.1 and 32.9cm, respectively. PHG was similar between SW and SV groups. PHG was related inversely to height at pubertal onset($p=0.03$) and positively to duration of puberty($p<0.05$). Peak growth velocity observed between Tanner II to III in both sexes. Median FH was 154cm(-1.5 SDS) in girls and 167cm(-1.5 SDS) in boys and was comparable to height predicted at Tanner II.

Conclusion: While mean age at onset of puberty is earlier, the tempo of puberty is slower and duration of puberty is prolonged leading to preserved pubertal height gain in patients with classical 21OHD.

P1-160

Serum fetuin-A and insulin levels in classic congenital adrenal hyperplasia

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Background: Androgens play a pivotal role in non-reproductive tissues, such as the kidney, heart, and liver, as well as the pancreas. Since the androgen receptor is expressed in pancreas and liver cells, this raises the possibility that excess testosterone results in insulin hypersecretion, and in fetuin-A, a protein produced in the liver. However, whether fetuin-A and insulin levels are affected by androgens in classic congenital adrenal hyperplasia (CAH) due to excess androgen exposure is unknown.

Methods: This research was designed as a cross-sectional study, and included 56 CAH subjects and matched controls. Measurements were performed on the basis of gender and of prepubertal/ pubertal status to eliminate potential changes in serum metabolic/ inflammatory markers associated with the production of sex steroids. CAH subjects and controls were then examined according to their clinical characteristics.

Results: Insulin and fetuin-A levels were significantly higher in the CAH patients than in the controls. Those unfavorable levels exhibited positive correlation with androgens, such as total and free testosterone. Multiple regression analysis revealed that total testosterone levels predicted fetuin-A and insulin levels in CAH patients ($r^2=0.39$, $p<0.001$; $r^2=0.36$, $p=0.027$). Differences were also observed in triglycerides and high-sensitivity C-reactive protein between the pubertal and prepubertal groups, respectively.

Conclusions: Serum fetuin-A and insulin levels are associated with androgens in CAH patients. It can be considered that androgens have indirect and direct effect on regulation of insulin.

P1-161

Perioperative control of blood pressure in a child with paraganglioma using Esmolol

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Background: Paragnagiomas and pheochromocytomas are rare neuroendocrine tumors that originate from the paraganglionic cells of the autonomic nervous systems. These tumors may be extra or intra-adrenal in site. The use of antihypertensive medications is usually challenging in these patients. Long acting alpha and beta blockade can be quite useful preoperatively but challenging postoperatively. We present a case of familial paraganglioma that was successfully treated by esmolol and other antihypertensive medications without associated perioperative complications.

Case Report: A 13-year-old girl, known case of bronchial asthma, presented with classic symptoms and signs of Pheo/Paragnagioma. She had impressive family history, and CT abdomen showed right-sided paravertebral mass, therefore, treated as familial paraganglioma. Prazocin was started but she continued to experience uncontrolled fluctuations of a high blood pressure (BP). She initially developed a serious reaction to atenolol, therefore switched to esmolol that successfully controlled her BP alongside prazocin and intermittent doses of hydralazine. She then underwent laparoscopic surgery and the diagnosis was confirmed by histopathology and genetic study.

Discussion: Preoperative management using Alpha and beta blockade is crucial to prevent the intraoperative complications in Pheo/Paragnagioma. Phenoxybenzamine, a long acting non-selective alpha blockade, has been widely used since 1950s. In addition, prazosin, a selective alpha 1 blockade, has been used in favor due to its short action, so it causes fewer side effects postoperatively. Beta blockade are generally used to suppress tachycardia, though they also help in control of BP, after alpha-blockers being started. There is no evidence to support the use of beta 1 blockade such as atenolol over the non-selective beta-blockers, which include propanol. Two previous reports suggested the use of esmolol in adults, yet, not in pediatrics as in our case. Esmolol showed a

good effect as adjuvant therapy to alpha-blockers and its very short half-life of approximately 3 minutes helped to avoid post-operative complications due to sudden intravascular volume and pressure changes that usually requires meticulous care and possible need of using presser agents.

Conclusion: Esmolol is titrable, effective and can be weaned rapidly helping to avoid post-operative complications in pediatric Pheo/Paraganglioma. Therefore, it can be a good alternative to propranolol and atenolol that are routinely used in these cases. Further study on its use is needed to confirm our observation.

P1-162

Evaluation of molecular characteristics and steroid metabolomics in a large cohort of children with 3 β -hydroxysteroid dehydrogenase 2 deficiency

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Context: Deficiency of 3 β -hydroxysteroid dehydrogenase 2 (3 β HSD2) causes a very rare form of congenital adrenal hyperplasia

(CAH) known as 3 β HSD2 deficiency, which is a consequence of biallelic *HSD3B2* gene defects. The estimated prevalence is less than 1/1,000,000 live births. Knowledge of comprehensive steroid metabolome patterns in 3 β HSD2 deficiency is scarce.

Objective: We aimed to investigate phenotypical, molecular, and biochemical characteristics, as well as the genotype-phenotype relationship in patients with 3 β HSD2 deficiency. We evaluated steroid hormone profiles in individuals with homozygous and heterozygous *HSD3B2* gene defects, mutation-negative “functional 3 β HSD2 deficiency”, and patients with 21-hydroxylase deficiency (21-OHD).

Setting: Multi-centre, cross-sectional study in nine tertiary pediatric endocrinology clinics in Turkey

Patients or Other Participants: Children with homozygous 3 β HSD2 deficiency (n=31), individuals with heterozygous 3 β HSD2 deficiency (n=31), children with classical 21-OHD (n=57), functional 3 β HSD2 deficiency (n=18), and healthy controls (n=172).

Main Outcome Measures: A structured questionnaire was used to assess clinical and biochemical phenotype data. Genetic analysis of *HSD3B2* was performed using Sanger sequencing. We measured Δ 5-to- Δ 4 steroids and 11-oxygenated C19 androgens in serum and urine by mass spectrometry. Novel *HSD3B2* mutations were studied *in silico* and by *in vitro* enzyme kinetic assays.

Results: We have identified 11 homozygous *HSD3B2* mutations (7 missense-4 novel, 2 novel deletions, 2 novel insertion variants) in 31 children from 24 families (19 male/12 female; mean age: 8.4±5 yrs). The missense variants >5% of wild-type 3 β HSD2 activity *in vitro* were associated with non-salt losing clinical phenotype. There was a strong genotype-phenotype-steroid metabolome correlation in patients with 3 β HSD2 deficiency. The plasma ratio of (17OH-Pregnenolone+Pregnenolone+DHEA)/(17OH-Progesterone+Progesterone+Androstenedione+Cortisol) was superior to (17OH-Pregnenolone/Cortisol) to discriminate 3 β HSD2 deficiency from the other groups. Heterozygote carriers and functional 3 β HSD2 deficiency patients showed higher Δ 5-to- Δ 4 steroids than controls. 11-oxygenated androgens were significantly lower in patients with 3 β HSD2 deficiency.

Conclusions: This largest pediatric cohort of patients with 3 β HSD2 deficiency will be of importance to gain a deeper understanding of the steroid metabolome and underlying molecular pathogenesis of 3 β HSD2 deficiency as well as the disease-specific complications of specific molecular genetic variants.

P1-163

Abstract withdrawn

P1-164**The urinary steroid signature of premature adrenarche**

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Background: Adrenarche describes the developmental event of the human adrenal cortex when the zona reticularis increases the synthesis of C19 steroids (DHEA/S) markedly at around 6-8 years of age. Early appearance of this event is called premature adrenarche (PA) and has been associated with adverse outcomes including polycystic ovary syndrome and metabolic syndrome. Recently novel biosynthetic pathways of androgen production have been revealed, but their role in health and disease remains largely unsolved.

Objective: This study aimed at characterizing the urinary steroid metabolome of girls with premature adrenarche in comparison to healthy controls with a special focus on metabolites originating of novel, alternate androgen pathways.

Methods: 39 steroid metabolites comprising progesterones, corticosterones, aldosterone, androgens, estrogens and glucocorticoids were measured in the urine by gas chromatography mass spectrometry in 23 girls with premature adrenarche (age range 3.9-8.4 years) and 22 healthy, age-matched controls (4.3-8.5 years). Groups were compared using Mann-Whitney test and Bonferroni correction applied to account for multiple testing.

Results: Girls with premature adrenarche were heavier (median weight 26.2 ± 4.5 kg) than controls (21.5 ± 3.4 kg) and had a higher BMI (17.2 ± 2.0 vs 15.0 ± 1.3 kg/m²) ($p < 0.001$). Gestational age and birth weight was comparable between groups. Steroid profiling revealed significant difference in overall androgen excretion, specifically the metabolites androsterone, etiocholanolone, dihydroandrosterone, dehydroepiandrosterone, androstenediol and androstenetriol were secreted in larger quantities in girls with premature adrenarche ($p < 0.001$). Some of these metabolites originate from alternate androgen pathways, e.g. androsterone. No differences were found in progesterones, corticosterones, aldosterone, estrogens and glucocorticoids. Ratio calculations for steroid enzyme activities suggested lower HSD3B2 activity in girls with premature adrenarche than in controls, while no difference was found for CYP21A2 activity.

Conclusions: Girls with premature adrenarche produce more androgens than healthy girls of the same age. The urinary steroid signature of adrenarche includes steroid metabolites of alternate pathways, which shows differences in premature adrenarche. Future studies should assess whether the steroid signature of adrenarche is just appearing earlier in girls with premature adrenarche or earlier and different compared to adrenarche at normal timing.

P1-165**How the level of antibodies against 21-hydroxylase changes with time in patients with Addison's disease**

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Objectives: To investigate changes in levels of auto-antibodies(Abs) against 21-hydroxylase(21OH) in APECED patients and in patients with isolated primary autoimmune adrenal insufficiency (AI) over time after manifestation of AI.

Methods: 24 patients with APECED with AI and 5 patients with isolated autoimmune AI were recruited. APECED was confirmed by finding at least two major components of the disease and/or two mutations in *AIRE* gene and/or high levels of antibodies against interferon- ω . APECED in patients with other forms of AI were excluded by performing genetic test and/or investigating antibodies against interferon- ω . All patients had been sampled twice. An interval time between samples was from 1 to 7 years in different patients. All blood samples were tested for autoantibodies against 21OH by ELISA.

Results: All patients had positive levels of Abs against 21OH in all their samples. But almost in all cases (24/29) levels of Abs were much higher in the first sample than in the second. Median of total percentage decrease of Ab's level was 55% [34;55] and median of percentage decrease of Ab's level per year was 18%[8;22]. Patients with longer duration of AI for the moment of first sample had lower level of Abs and more gradual percentage decrease. Only one patient had the same level of Abs in both samples with interval 5 years between them. Levels of Abs increased by 44% in one patient, who had only 1 year duration of AI at the time of sampling. Additionally two patients had unsignificant increase of levels of Abs (11% and 15%), both patients had AI during 12 years before the sampling.

Five patients had positive antibodies, but the level was near the borderline, and duration of AI in all of them was more than 15 years.

Conclusions: Reactivity against of 21OH was decreasing over time in most of patients with autoimmune AI, but in all tested patients the level of antibodies remained positive (above the cutoff) up to 19 years after manifestation of AI. Detection of Abs against 21OH could be reliable method for differential diagnosis of autoimmune AI even in patients with long-lasting AI.

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P1-166**Cortisol levels in glucagon stimulation tests in children evaluating for short stature: clinical and laboratorial correlations**

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Background: Glucagon stimulation test (GST) is used to assess growth hormone (GH) and cortisol reserves in children being investigated for GH deficiency, as a small percentage of children with idiopathic GH deficiency can also exhibit deficiency in the adrenocorticotropic hormone (ACTH)-cortisol axis. However, the extent of normal cortisol response after glucagon stimulation and its associations with clinical and laboratory parameters have not been thoroughly studied.

Aim: To assess total cortisol levels in children being evaluating for short stature with normal cortisol reserve and to correlate this response to clinical and laboratory data.

Patients and Methods: During the last 5 years, children assessed with glucagon test in our department were recruited retrospectively. Inclusion criteria were: *i*)age > 1 year, *ii*)absence of chronic illness or medication interfering with ACTH-cortisol axis, *iii*)GH stimulation levels > 3ng/mL at least in one provocation test (glucagon or clonidine), *iv*)absence of multiple pituitary growth hormone deficiencies, *v*)normal short Synacthen test in cases of low cortisol response in glucagon test. Glucagon tests were performed after an overnight fasting with the intramuscular administration of glucagon (0.03 mg/kg, max: 1mg). Blood samples were drawn with 30 minutes intervals until 180 minutes for the assessment of GH, total cortisol and glucose levels and the calculation of area under the curve (AUC).

Results: Two hundred and thirty-seven subjects (160 males, 67,5%) were finally included in the analysis. Mean age at the time of the evaluation was 9.02 ± 3.19 years (range: 1.86 – 16.45 years). Cortisol peak levels but not cortisol AUC were significantly increased in females compared to males (26.83 ± 7.31 μ g/dL versus 24.04 ± 7.20 μ g/dL). When linear correlations were studied, both cortisol peak levels and cortisol AUC were linearly but inversely correlated to age ($r=-0.234$, $p<0.001$ and $r=-0.315$, $p<0.001$, respectively). Finally, cortisol AUC was inversely correlated to weight Z-scores ($r=-0.160$, $p=0.014$).

When our analysis was limited only to subjects with intact GH response (GH peak > 7ng/ml), age was still inversely correlated to cortisol AUC ($r=-0.312$, $p<0.001$), and cortisol AUC was linearly correlated to GH AUC assessed with clonidine test ($r=0.223$, $p=0.013$).

Conclusions: Girls and younger children seems to exhibit higher cortisol response to glucagon test, whereas younger and leaner subjects show also greater cortisol response. In subjects with intact GH reserve, a greater cortisol response in glucagon test was linearly correlated with a greater GH response in clonidine but not in glucagon test.

P1-167**Development Of An International Benchmark For Sick Day Episodes As A Core Clinical Outcome In People With Congenital Adrenal Hyperplasia**

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Background: Congenital adrenal hyperplasia (CAH) is a rare condition characterised by adrenal insufficiency and a life-long risk of adrenal crises. There is a paucity of information on the epidemiology of acute adverse events in this population.

Objective: To investigate the frequency, aetiology and consequences of acute adverse events attributed to adrenal insufficiency in CAH.

Methods: A longitudinal analysis of patients with CAH in the International Congenital Adrenal Hyperplasia Registry (I-CAH registry, www.i-cah.org) which collects information on acute adverse events including sick day episodes and adrenal crises.

Results: 509 patients (n= 478, 21-OHD) from 31 centres in 16 countries and a total of 3880 visits were evaluated. 261 patients (n=255, 21-OHD) had one or more sick day episodes (684 visits); of these, 215 (82%) were less than 18 years of age. 1034 sick day episodes were recorded in total, with 920 (89%) episodes recorded in those less than 18 years of age. The overall median number of sick day episodes for all centres per patient year was 3.0 for children (IQR 1.7-4.7) and 3.9 for adults (IQR 1.8-10.2) (p=0.26). The median duration of sick day episodes was 3 days (IQR 2.0-5.0) and 2 days (IQR 1.0-3.0) in children and adults respectively (p<0.05). During childhood, younger age and low hydrocortisone dose (mg/m²/day) were associated with a greater number of sick day episodes (p<0.01). Female sex was associated with higher rates of admission amongst both children and adults (p<0.01). Infectious illness was the most frequent event causing illness episodes and adrenal crises in both children (66%) and adults (23%). An adrenal crisis was reported in 37 (4%, 37/920) and 34 (30%, 34/114) sick day episodes amongst children and adults, respectively (p<0.05) and all adults required hospital admission.

Conclusions: The real world data within the I-CAH registry are a valuable resource for studying a core clinical outcome that can be used as a benchmark for improving clinical care. Further work needs to be undertaken to understand the determinants of the observed variations in the occurrence of sick day episodes.

Bone, Growth Plate and Mineral Metabolism

P1-168

Genotype-phenotype characteristics in four families of type II collagenopathy in our hospital

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Type II collagenopathy is a generic name of the skeletal dysplasia caused by *COL2A1* gene, such as achondrogenesis type II, spondyloepiphyseal dysplasia (SEDC), spondyloepimetaphyseal dysplasia (SEMD). Since this is a rare disease, genotype-phenotype characteristics is still unclear. Here, we describe the genotype-phenotype characteristics of four families of type II collagenopathy in our hospital. Family 1: the proband was 2-year-old girl. She showed severe short stature (-4.1 SD), flat nose, platyspondyly, barrel chest and femoral epiphysis enlargement. SEDC was suspected. Her father and her younger sister also showed the same phenotype. Novel heterozygous splice site mutation. (c.3436-2 A>G) was identified in the family. Family 2: the proband was 2-month-old boy. He presented short limbs in the prenatal period and presented flat nose, short stature (-5.0 SD), platyspondyly, hypoplastic ileum and delayed ossification of the pubis and femur at the first visit. SEDC or SEMD was suspected. His parents presented no symptoms. The heterozygous mutation (c.3121 A>G) was found in the proband. This is a glycine substitution mutation. Family 3: 6-year-old boy and 4-year-old girl had flat noses, small jaws, severe short stature (-8.5 SD and -10.0 SD) and short limbs. They presented respiratory distress at birth. Their radiograph showed small chest, oval vertebra, hypoplastic ileum, delayed ossification of pubis and dumb-bell like femurs and humerus. SEMD or Knist dysplasia was suspected. The heterozygous mutation (c.3121 A>G) was found in the two patients. This is also a glycine substitution mutation. Family 4: the proband was a boy one day after birth. He presented short limbs in the prenatal period. At birth, mild respiratory distress was presented. He showed hyperterolism, mid face hypoplasia, short trunk short stature (-4.0 SD), platyspondyly, hypoplastic ileum and delayed ossification of the pubis and femur. Hypochondroplasia was suspected, and he was treated with growth hormone. The novel heterozygous carboxyl-terminal region mutation (c.4454G>C) was detected in the proband. Although the splice site mutation was associated with mild phenotype, such as Stickler syndrome, family 1 was severe short stature. The glycine substitution in triple helix of type 2 collagen is related with severe phenotype. Thus, both family 2 and 3 presented severe short stature, but the severity was different. While a C-terminal region mutation was identified in platyspondylic lethal skeletal dysplasia Torrance type, other phenotypes have been reported like family 4. It is important to assess not only the phenotype but also the genotype in a medical examination of type II collagenopathy

P1-169**Hypercalcemia as a post stem cell transplantation complication in children with osteopetrosis - A single centre experience**

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Introduction: Osteopetrosis (OP) is a rare genetic disorder that is characterized by abnormal osteoclast function resulting in dense bones and marrow failure. The only definitive cure for OP is stem cell transplantation (SCT). Hypercalcemia is a well described complication in children with OP undergoing SCT. This study describes the calcium profile and treatment modalities used to maintain normocalcemia in children with OP undergoing SCT.

Aim: To study the calcium profile of all patients with OP who underwent SCT from 2012 till date at our institution.

Results: Five children (all males) with OP underwent SCT at a median age of 10 months (9-22months). Baseline median serum calcium was 8.3 mg/dl (7.3-8.9mg/dl). Source of graft was peripheral blood in 1 child and bone marrow in 4 children. Hypercalcemia (serum calcium >11mg/dl) developed in 2/5 at a mean of +12 days post SCT. Of the two, one child aged 12 months with negative genetic studies developed hypercalcemia for 8 days (peak S.calcium 15.62mg/dl). The second child aged 22 months with positive TNFRSF11A gene mutation has ongoing hypercalcemia at +270days post SCT (peak S.calcium 16.8 mg/dl). Hypercalcemia was managed with forced diuresis, corticosteroids, calcitonin and Pamidronate with the second child receiving Cinacalset in addition. A third child aged 9 months maintained normocalcemia with forced diuresis for an increasing trend of serum calcium level (from 7.3 to 10.7 mg/dl). Of the three children who maintained normal calcium level post SCT, 2 were positive for TCIRG1 and CLCN7 mutation respectively, and 1 had negative genetic studies. 1 of these 3 children expired of sepsis and multiorgan failure on day +33 post SCT.

Discussion: Despite a low/normal baseline serum calcium level and lower age, hypercalcemia occurred in 40% children with OP undergoing SCT in our centre as compared to other studies(1). The duration of hypercalcemia was variable. The efficacy of Cinacalset and long term effects of bisphosphonate therapy in this setting remains unclear.

Conclusion: Hypercalcemia is an expected complication in children with Osteopetrosis undergoing SCT. Both the absolute serum calcium level and its rising trend must be monitored closely in these children. The onset, duration and severity of hypercalcemia is variable and may require multiple pharmacological agents to maintain normocalcemia. Further studies are needed to assess predictors for hypercalcemia and establish genotype-phenotype correlation to understand risk factors for life-threatening hypercalcemia.

Reference

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P1-170**Efficacy and safety of denosumab treatment in a boy with cherubism**

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Introduction: Denosumab is an inhibitor of receptor activator of nuclear factor kappa-B ligand that strongly suppresses differentiation and function of osteoclasts. Cherubism is a rare autosomal dominant disorder characterized by symmetrical swelling of the mandible and the maxilla. In patients with cherubism, the bone is replaced by a fibrous granuloma containing multinucleated giant cells, which are differentiated into activated osteoclasts.

Objective: To report efficacy and safety of a 6-month treatment with denosumab in a child with cherubism.

Case Report: The Japanese boy was firstly diagnosed as cherubism at 4.5 years of age because of bilateral swelling of the lower jaw and a family history of the same disorder in his father. A heterozygous hot spot mutation for cherubism in the SH3BP2 gene (c.1253C>G, p.Pro418Arg) was identified in the patient by Sanger sequencing. At 9 years of age, he was referred to us because of progressive swelling of the jaws and delayed permanent teeth eruptions. The panoramic radiographs and computed tomography revealed expansive multiple cystic formations of the mandible and the maxilla and buried multiple permanent teeth. Because surgical treatment seemed to be difficult, he underwent denosumab treatment, consisting of 8 doses of subcutaneous denosumab injections (120 mg/dose) at day 0, day 7, day 28, and every 4 weeks thereafter for 6 months. The 6-month treatment suppressed the expansion of the cystic lesions that were dramatically ossified. Not only a bone resorption marker (urine NTx/Cr) level but also a bone formation marker (BAP) level quickly decreased upon the treatment and gradually increased 4 months off treatment. Upon treatment, he developed mild asymptomatic hypocalcemia that was controlled quickly after replacement of alfalcacidol. His growth chart showed decreased growth rate during a period from the initiation of the treatment to 5 months after the discontinuation. Other side effects, such as bone necrosis, have not been observed in the patient.

Conclusions: The present case demonstrated for the first time the therapeutic potential of denosumab for treatment of cherubism, although adverse impacts, especially on childhood growth, remain obscure. Further studies are needed to establish the safe and effective protocol of denosumab treatment for children.

Evaluation of bone health in adolescents and young adults after allogeneic human stem cell transplantation in childhood: a single center cross-sectional study

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Introduction: Hormonal deficits are well known complications after allogeneic human stem cell transplantation (alloHSCT) in childhood and treated according to existing guidelines. It is assumed that bone mass and strength accrual during puberty is also often impaired, due to toxic therapy and prolonged inactivity, but data on bone geometry and strength are scarce in this particular group.

Objective/Patients and Methods: Cross-sectional study of bone health in boys and girls (aged 15-25 years) who received HSCT in childhood, as compared to healthy controls. All cases received allo HSCT for a hematological malignancy. Bone mass, size and density (BMD) were determined by dual-energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT). Statistical analysis was performed using SPSS (version 25): Mann-Whitney U-Test and unpaired student-t Test, as appropriate.

Results: Twenty-two cases (11 males) and 22 healthy controls (11 males) participated. Mean age at time of alloHSCT was 9.2 ± 4.91 years and mean interval since alloHSCT was 10.9 ± 4.57 years. DXA results revealed no significant difference in whole body BMD (wbBMD) and lumbar spine BMD in female patients as compared to controls ($p=0.916$ and 0.475 , respectively). pQCT scans in females revealed comparable results with no difference in trabecular vBMD, cortical vBMD, periostal and endosteal circumferences and polar strength strain index (SSI_P) between patients and controls (NS). In male patients, wbBMD was significantly lower in patients as compared to controls ($p=0.003$). Lumbar spine BMD was also lower but did not reach significance ($p =0.058$). Male patients had a lower tibia and radius cortical thickness ($p=0.035$ and 0.026 respectively), mainly due to a smaller periostal circumference ($p=0.032$) and a lower tibia and radius SSI_P ($p=0.003$ and 0.015 , respectively).

Conclusion: Young adults, several years after HSCT in childhood, are at risk for suboptimal bone mass in comparison with a control group. Our data highlight the need for life style interventions post alloHSCT aimed at optimizing bone health.

Is serum alkaline phosphatase useful in assessing rickets severity on radiographs in children with X-linked hypophosphataemia on conventional therapy?

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Introduction: Conventional treatment of X-linked hypophosphataemic rickets (XLH) involves administration of oral phosphate and vitamin D analogues. An important treatment goal is to heal rickets which is assessed by normalisation of serum alkaline phosphatase (ALP) levels and resolution of radiological signs of rickets.

Objectives: To determine the usefulness of serum ALP in assessing disease severity on wrist and knee radiographs as determined by rickets severity scores (RSS) and Thacher scores.

Methods: Patients from 3 UK tertiary centres, with a confirmed diagnosis of XLH (documented *PHEX*mutation in the patient or family member) and ≥ 3 radiographs were included. Data was collected retrospectively from case notes and electronic database. Radiographs were scored for RSS and Thacher scores by a consultant in metabolic bone disease (RP) and radiologist (RS). Due to different assays used for ALP measurements, ALP z scores were calculated using age- and sex-specific mean/standard deviation (SD) lab specific reference data. Wilcoxon Signed Ranks test was used to compare knee and wrist RSS. Spearman's correlation was used to determine the relation between ALP z scores and Knee RSS and Thacher scores.

Results: Forty (male=12) patients with a median age of 9.3 years (range 0.8-18.9) were identified. Median age at diagnosis was 1.17 years (range 0.2-11.7). The majority (48%, n=19) were diagnosed within the first year of life. The median follow-up duration was 7.2 years (range 0.6-18.7). The mean \pm SD knee RSS and Thacher score at baseline were 1.9 ± 1.2 (n=19) and 3.3 ± 1.3 (n=8) respectively and at most recent follow up visit were 1.6 ± 1.0 (n=26) and 2.4 ± 1.6 (n=6). The mean \pm SD ALP z score at diagnosis and most recent visit were 4.2 ± 2.9 (n=36) and 4.1 ± 2.7 (n=34). The wrist RSS was significantly lower than the knee ($p<0.001$). There was no significant correlation between ALP z score and knee RSS ($r=0.17$) or wrist RSS ($r=0.32$) or Thacher scores ($r=0.14$).

Conclusions: 1. Conventional therapy was not effective in significantly improving biochemical and radiological features of disease. 2. Lack of association between serum ALP and rickets severity on radiographs limits the value of serum ALP as the sole indicator of rickets activity.

P1-173**Cutoff value for 25 Hydroxy-vitamin D which leading to symptomatic vitamin D deficiency in children is 15 ng/mL in a chemiluminescent immunoassay**

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Background & Purpose: Vitamin D is essential for bone and calcium metabolism, and a deficiency of this nutrient can lead to rickets and hypocalcemia. A 25 hydroxy-vitamin D (25OHD) value below 12 ng/mL (30 nmol/L) has been established by global consensus on the basis of several studies as constituting vitamin D deficiency. For example, (1) the incidence of nutritional rickets can increase at a 25OHD concentration of less than 12 ng/mL; (2) PTH increases when the 25OHD level is below 13.6 ng/mL, etc. No studies have yet analyzed the association between the 25OHD value and the occurrence of rickets and hypocalcemia due to vitamin D deficiency. We herein aimed to examine the association between 25OHD levels and the symptoms of vitamin D deficiency by receiver operation characteristic (ROC) analysis.

Method: We conducted a retrospective study from April 2013 to March 2018 at four hospitals. All subjects aged 0 to 15 years who were screened for vitamin D deficiency were recruited.

Results: Chemiluminescent immunoassay (CLIA) was used to measure the 25OHD levels in 605 subjects. Of these, 408 subjects were excluded due to having a cause of rickets or hypocalcemia other than vitamin D deficiency or for having already received treatment. As a result, 197 subjects (92 males) ranging in age from 0.1~14.8 years were analyzed. Of these, 117 (59.4%) were asymptomatic, 11 (5.6%) had healing rickets, and 69 (35.0%) were symptomatic (had received the diagnosis of rickets or hypocalcemia). The 11 patients with healing rickets were excluded from the analysis.

First, ROC analysis was performed. The cut-off value for 25OHD for the asymptomatic group (n=117) and symptomatic group (n=69) was 15.0 ng/mL, and the sensitivity and specificity was 73% and 99%, respectively (AUC: 0.880, 95% CI: 0.831-0.929).

Next, a sub-analysis of ROC was done due to a statistical difference in the U-Ca/Cr levels between the asymptomatic and symptomatic groups. When the 25OHD value was calculated separately for subjects with U-Ca/Cr \geq 0.1 (n=50) and <0.1 (n=78), the cut-off value of 25OHD, similarly obtained, was 15.0 ng/mL and 9.3 ng/mL, respectively.

Discussion & Conclusion: Our study found that the 25OHD cutoff value leading to symptomatic vitamin D deficiency was 15 ng/mL on CLIA. The findings suggest that low U-Ca/Cr, which may reflect Ca intake, modifies the manifestation of rickets and hypocalcemia.

P1-174**The Optimal Dosage of Vitamin D Supplement for Vitamin D deficiency in Korean Children and Adolescents**

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Purpose: Vitamin D deficiency (VDD) is very common nowadays in children as well as in adults, probably due to decreased exposure to sunlight. In Korea, the prevalence of VDD was 47% in teenage boys and 65% in teenage girls. However, the optimal dosage regimen for correcting deficiency is unknown. We investigate the change of serum 25(OH) vitamin D concentration according to the treatment dosage and duration in VDD.

Methods: Data was collected from 1797 children and adolescents aged 0 to 16 year between August in 2017 and July in 2018, retrospectively. They were divided to 3 groups (deficiency, insufficiency, sufficiency) according to their serum 25(OH) vitamin D concentrations (less than 20, between 20 and 30, more than 30 ng/mL, respectively). There were 3 subgroups (poor, moderate, good) according to the daily increase (DI) of the serum 25(OH) vitamin D concentration (less than 0.3, between 0.3 and 0.6, more than 0.6 ng/mL/day, respectively) after 4 to 6 week oral administration of 25(OH) vitamin D in children and adolescents with vitamin D deficiency.

Results: The serum 25(OH) vitamin D concentration showed the correlation with age ($p=0.000$), gender ($p=0.000$), weight standard deviation score (SDS) ($p=0.008$) and body mass index (BMI) SDS ($p=0.000$). And the serum 25(OH) vitamin D concentration showed seasonal variation in children over 2 years of age and adolescents ($p=0.000$). There was a significant correlation between serum 25(OH) vitamin D concentration and DI ($p=0.021$). In VDD patients treated with vitamin D, DI were not correlated with age, sex, weight SDS and BMI SDS.

Conclusions: The prevalence of VDD increased in female, older age, overweight and winter in Korea and the response to treatment was higher in patient with lower serum 25(OH) D concentration. It may be appropriate to take an oral 25(OH) Vitamin D with 2000 IU/day for 6 weeks in Korean children and adolescents with VDD.

Rare Causes of Osteogenesis Imperfecta are Common in Consanguineous Pedigrees

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Background: Osteogenesis imperfecta (OI) is characterized by low bone mass and bone fragility mainly due to *COL1A1/COL1A2* gene defects. However, >17 genes have been identified in the pathogenesis of OI. Here, we aim to characterize genotypic spectrum of our OI cohort.

Methods: Forty-nine OI patients (28 males) from 38 different families (13 consanguineous/9 multiplex) were screened with the next-generation sequencing (NGS) panel for 15 OI genes and, Sanger sequencing was used for confirmation and segregation analyses. Sillence classification was used to define clinical severity.

Results: We have identified *COL1A1* (n:14, 5 novel) and *COL1A2* mutations (n:3) in 22 patients from 18 unrelated families. *FKBP10* mutations had been detected in 9 patients from 6 families. Four patients from 2 families also had Epidermolysis Bullosa. They had co-segregated founder mutations in *FKBP10* (p.Met107_Leu117del) and *KRT14* (p.Tyr204*) genes which were reported previously in patients from the same geographical region as our patients. Additional four patients from 4 families had 3 novel *FKBP10* mutations, interestingly, one OI-3 patient had a brother with Bruck syndrome who were carrying same mutation.

Three novel homozygous *P3H1* mutations had been identified in three patients who had typical features of round face and long fingers. A novel homozygous *SPARC* mutation was identified in two siblings. We have also identified a paternally inherited heterozygous *IFITM5* mutation in one patient. Additionally, a homozygous *WNT1* mutation in one patient with congenital ptosis, a novel homozygous mutation in *CRTAP* in one patient, *BMP1* in two patients from one family and *SERPINF1* in one patient had been detected (Table).

Conclusions: We were able to identify the molecular etiology in 79% of our OI cohort by NGS panel and detected 15 novel mutations in 7 different genes. And, 35% of the defects were in non-*COL1A1/COL1A2* genes and 80% of them coming from consanguineous families.

Sillence Types	Gene; Mutation	N individuals M/F	Blue Sclera (+)	Dentinogenesis Imperfecta (+)
OI-I	<i>COL1A1</i> ; p.Gly260Asp, p.Gly329Val, p.Gly560Ser, p.Gln202Ter, p.Ala714Profs*6, p.Ala1256Profs*75, IVS2+1G>A, IVS5+1G>A, IVS17 +1 G>C	6/6	12	6
	<i>COL1A2</i> ; p.Gly601Ser, IVS15-2A>G	2/0	2	2
	Unknown	1/0	1	0
OI-II	<i>COL1A1</i> ; p.Gly704Ser	1/0	1	NE
	<i>COL1A1</i> ; p.Gly1076Ser, p.Gly413Leufs*122	0/2	2	NE
OI-III	<i>COL1A2</i> ; p.Gly773Ser	1/0	1	1
	<i>SPARC</i> ; p.Glu54*	1/0	1	0
	<i>P3H1</i> ; p.Met206Ile, c.941-1G>A	1/1	3	2
	<i>WNT1</i> ; p.His267Profs*30	1/0	1	1
	<i>LRP5</i>	1/0	*pseudoglioma	1
	<i>SERPINF1</i> ; p.Ile301Argfs*21	1/0	0	1
OI-IV	<i>FKBP10</i> ; p.Met107_Leu117del, p.Gly300Ter, p.Leu105_Arg-115del, p.Ser8Glnfs*67	5/3	4	2
	<i>COL1A1</i> ; p.Gly218Asp, p.Arg598Ter	0/4	4	3
	<i>SPARC</i> ; p.Glu54*	1/1	2	0
	<i>CRTAP</i> ; p.Glu179Ter	1/0	1	1
	<i>BMP1</i> ; p.Arg371His	2/0	0	0
OI-V	<i>P3H1</i> ; p.Leu149Arg	0/1	1	0
	Unkonwn	3/0	3	1
	<i>IFITM5</i> ; c.-14C > T	0/1	1	1
BruckSyndrome Type 1	<i>FKBP10</i> ; p.Ser8Glnfs*67	1/0	1	1

Genotype and Phenotype Characterization of Turkish Patients with Vitamin D Dependent Rickets Type IA

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Background: Vitamin D Dependent Rickets Type IA (VDDR-IA) is the most common type of VDDR and caused by mutations in *CYP27B1*. Here, we aimed to analyze the genotypic and phenotypic features of our VDDR-IA patients.

Materials and Methods: The patients with a clinical diagnosis of VDDR-IA were enrolled and analyzed for *CYP27B1* gene mutations.

Results: 12 (5 males) patients from 9 unrelated families were evaluated. The mean age of diagnosis was 3.48 ± 4.00 (median: 1.1 ; min-max: 0.75-11.6) years. Patients were initially misdiagnosed as nutritional (n:7) or hypophosphatemic rickets (n:3) before referral to our clinic. All had biochemical evidence suggestive of VDDR-IA (Table), except one with hypocalcemia and hyperphosphatemia (Ca: 6.4 mg/dL; PO4: 6.2 mg/dl; ALP: 710IU/L; PTH: 362 pg/ml;

25-OH vit D: 34 ng/ml), in whom pseudohypoparathyroidism (PHP) was excluded with normal *GNAS* gene sequencing and *Gsa* levels. Then, VDDR-IA was subsequently considered upon bone pain and the radiological findings of rickets on initial presentation. Six patients had a history of high dose vitamin D intake (300000-1500000 IU) and one had toxic level of 25[OH]D (250ng/ml). Mutation analysis of *CYP27B1* gene revealed a homozygous frameshift mutation (p.Phe443Profs*24) in 6 patients from 4 unrelated families, and a homozygous missense mutation (p.Lys192Glu) in 3 patients from 2 unrelated families. Homozygous p.Phe443Profs*24 mutation leads to a truncated protein without enzymatic activity and the patients with this mutation presented to the clinic at an earlier age than the patients with p.Lys192Glu mutation (1.12 ± 0.31 vs 10.13 ± 1.40 years). A homozygous p.L380Afs*57 mutation was detected in one patient. Molecular analysis of two patients is still in progress .All mutations reported in our patients represent previously reported regional founders, which potentially facilitate genetic testing in VDRR-IA patients with same geographical origin.

Conclusions: Our results indicate a good genotype-phenotype correlation in patients with VDDR-IA and emphasize the importance of correct diagnosis in VDDR-IA for the proper management, and avoiding poor clinical outcomes.

	Mean ± SD	Min - Max	Reference
Ca (mg/dL) n=12	7.69 ± 1.65	4.8 - 10.3	8,4-10,2
P (mg/dL) n=12	3.08 ± 1.08	2.2 - 6.2	2,4-10,4
ALP (IU/L) n=12	2197 ± 2339	219 - 9251	46-110
PTH (pg/ml) n=11	513 ± 323	121 - 1006	15-65
25OHD (ng/ml) n=11	86.5 ± 73.1	24 - 250	20-100
1,25(OH)2D (pg/mL) n=8	33.3 ± 27.5	<8 - 85.9	16-65

P1-177

Severe Hypocalcaemia in Propionic Acidaemia caused by Parathyroid Hormone Resistance and treated with Alfacalcidol

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Introduction: Propionic Acidaemia (PA), an organic aciduria, is characterized by episodes of decompensation with severe metabolic acidosis and hyperammonaemia. PA is associated with low bone mineral density and osteoporosis. Hypocalcaemia is known to occur in 35-65% of decompensations, however the underlying pathophysiology remains unclear. PTH resistance has previously only been described in one case of hypocalcaemia in PA and we report the first use of alfacalcidol in the management of this complication.

Case: A term female infant presented on day 3 with grunting, acidosis and hyperammonaemia, with subsequent diagnosis of PA. She was hypocalcaemic (1.32mmol/L) with a profile suggestive of PTH resistance: normal phosphate 1.8mmol/L and magnesium 0.78mmol/L, low alkaline phosphatase (ALP), 77IU/L, and high parathyroid hormone (PTH) 115ng/L. Vitamin D was low 29nmol/L, but disproportional to the degree of hypocalcaemia. Serum calcium normalized with intravenous calcium and oral cholecalciferol.

At 2.5 months, she decompensated secondary to an infection with vomiting, lethargy and jitteriness. Bloods showed acidosis, hyperammonaemia, and hypocalcaemia (1.56mmol/L) with associated PTH resistance: normal vitamin D 91nmol/L, phosphate 1.6mmol/L, magnesium 0.68mmol/L, and ALP 227IU/L, elevated PTH 297ng/L and urine calcium:creatinine ratio 2.75, and low urinary phosphate <1.1mmol/L.

She was managed on intravenous fluids and ammonia scavenger drugs with feeds restarted on day 2. Calcium normalized after treatment with oral calcium (1.25mmol/kg/day), cholecalciferol (3000 units/day) and a magnesium infusion.

Alfacalcidol was started (30ng/kg/day), and oral calcium and cholecalciferol was reduced. Calcium fell (2.5 to 2.01mmol/L) after cessation of calcium supplements, but normalized rapidly (2.56mmol/L) after alfacalcidol was increased to 60ng/kg/day.

Discussion: PTH resistance appears to be the mechanism for hypocalcaemia during episodes of PA decompensation. Acute management of PTH resistance includes active vitamin D (calcitriol or alfacalcidol) and adequate calcium supplementation.

A retrospective chart review of our unit showed that 4 of 6 children had hypocalcaemic episodes (range 1.19-2.01mmol/L) associated with PA decompensation. Out of a total of 25 episodes of decompensation, 9 were associated with hypocalcaemia with normal/slightly low phosphate and ALP. No hypocalcaemia was recorded when patients were well, however routine monitoring was not undertaken. Only in our case was PTH measured and treated with alfacalcidol.

We propose that intermittent PTH resistance may contribute to bone demineralisation in PA. Further studies assessing the mechanism of this and potential utility of ongoing treatment with alfacalcidol would be valuable in guiding long-term management of bone health in PA.

Diabetes and Insulin

P1-178

The Efficacy and Safety of Predictive Low Glucose Suspend Feature in Decreasing Hypoglycemia in Children with Type 1 Diabetes Mellitus: a systematic review and meta-analysis

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Background: Hypoglycemia is a common side effect of insulin replacement therapy in patients with type 1 diabetes mellitus (T1DM). With the advancement of diabetes technology, sensor-augmented pump therapy (SAP) with predictive low glucose suspend feature offers a potential solution for hypoglycemia in patients with T1DM. However, evidence from randomized trials about the efficacy and safety of PLGS is limited.

Method: We did a systematic search and included randomized trials evaluating the effect of SAP with PLGS feature compared with SAP or insulin pump therapy in decreasing hypoglycemia in children and adolescents with type 1 diabetes mellitus, with at least two weeks of follow-up. Two review authors independently selected studies, extracted data and evaluated the risk of bias using the Cochrane 'Risk of bias' tool.

Results: We included five RCT with a total sample size of 493 patients and studies duration ranged between two weeks and 6 months. All the included studies have at least one domain with a high risk of bias except one study with a low risk of bias. There is low quality evidence that PLGS is superior to SAP in decreasing % of hypoglycemia <3.9 mmol/l/24 hrs with absolute mean difference of 17 minutes/day (19 min lower-15.3 min lower) and moderate quality of evidence that PLGS is superior to SAP in decreasing % of nocturnal hypoglycemia <3.9 mmol/l/ with absolute mean difference of 31.9 minutes/day (44 min lower-19.7 min lower) without increasing percentage of hyperglycemia or events of diabetic ketoacidosis. However, there was no statistically significant reduction of severe hypoglycemia <2.8 mmol/l and no enough evidence regarding the long-term effects of PLGS.

Limitations: Most of the studies were open-label studies with risk of cointervention and ascertainment bias. Four out of five studies had a short duration with no evaluation of long term effects of PLGS.

Conclusions and Implications of key findings: In children and adolescents with T1DM, PLGS is superior to SAP in decreasing hypoglycemia <3.9 mmol/l and nocturnal hypoglycemia <3.9 mmol/l without increasing the risk of DKA or hyperglycemia. There is no difference between SAP and PLGS in decreasing severe hypoglycemia and no enough evidence to test the long-term effect of PLGS.

Longitudinal metabolic control after initiation of insulin pump in 5,040 pediatric type-1-diabetes subjects – heterogeneous HbA1c trajectories over three years from the DPV registry

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Objectives: Continuous subcutaneous insulin infusion (CSII) has been associated with lower HbA1c. To explore whether CSII initiation leads to HbA1c improvement in each individual with

type-1 diabetes and to identify co-variates which might influence change in HbA1c.

Methods: 5,040 pediatric type-1-diabetes subjects (≤ 20 y, 49% boys, median age at diabetes onset [Q₁;Q₃]: 5.9 [3.5;8.4] years) with diabetes duration ≥ 3 years at CSII initiation (median initiation year: 2009) and continuously documented pump therapy over three years were selected from the DPV registry. Group-based modeling was applied to identify heterogeneous subgroups of HbA1c change after CSII initiation (SAS: PROC TRAJ; HbA1c values aggregated quarterly; patients with <7 aggregated values excluded). HbA1c change (D) was defined as HbA1c at the respective time-point minus baseline value.

Results: Four different trajectories of HbA1c change were identified (table1). Group 1 had a HbA1c reduction within the first quarter of the year which persisted thereafter, while group 4 had a dramatic HbA1c increase during the three-year observation period. Group 2 had a slight reduction and group 3 a slight increase of HbA1c. Age at diabetes onset, age and HbA1c at CSII initiation and insulin dose were all related to group membership (each $p < 0.001$). At CSII initiation, group 1 had the highest HbA1c and was oldest (table1). Further, they were oldest at diabetes onset and had highest insulin requirements. Analyzing boys and girls separately, the same number of trajectory groups was revealed, although gender ratio differed. In girls, the largest group (47%) had a slight HbA1c increase, whereas in boys (43%) the largest trajectory revealed a slight decrease.

Conclusions: There are different trajectories of HbA1c change after start of CSII in pediatric type-1-diabetes patients. Further analyses are needed to characterize the subgroups in order to predict which patients may be most successful in terms of HbA1c with insulin pumps.

Table 1. Group-specific characteristics of the four different Δ HbA1c trajectories

	Group 1 ($\Delta -2\%$)	Group 2 ($\Delta -0.25\%$)	Group 3 ($\Delta +0.8\%$)	Group 4 ($\Delta +2.5\%$)
N	346 (7%)	1,950 (40%)	2,296 (44%)	448 (9%)
Age at diabetes onset, years	6.7[3.7;9.9]	5.7[3.4;8.3]	5.9[3.5;8.3]	6.6[4.0;8.8]
Age at CSII initiation, years	14.2[12.0;15.6]	12.4[10.1;14.4]	12.2 [10.2;14.2]	13.1[11.5;14.6]
HbA1c at CSII initiation, %	9.7[9.0;10.7]	7.9[7.3;8.5]	7.3[6.7;7.9]	7.4[6.7;8.2]
Insulin dose after CSII initiation, IU/kg*d				
1 year	0.85[0.72;1.01]	0.78[0.66;0.94]	0.78[0.65;0.93]	0.82[0.69;0.98]
2 years	0.87[0.72;1.01]	0.79[0.66;0.94]	0.80[0.67;0.96]	0.87[0.71;1.05]

P1-180**Efficacy and Safety of Insulin Degludec as a basal insulin in adolescents with Type 1 Diabetes during Ramadan fasting: A single center observational study with freestyle libre flash glucose monitoring system**

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Background: Insulin degludec (IDeg) is an ultra-long-acting insulin, with flat time-action profile, having a lower risk of hypoglycemia. Many adolescents with type 1 diabetes, choose to observe Ramadan fasting for spiritual wellbeing despite different risks.

Aim of study: To assess frequency, timing and severity of hypoglycemia of insulin IDeg as basal insulin in T1DM adolescence who are willing to fast. Other outcomes included glycemic control, number of days needed to break fasting, and acute glycemic complications.

Methods: Thirty eight patients (19 males) with T1DM (mean age 15.8 ± 3.4 years) and duration of diabetes (5.2 ± 1.7 years) were included. Patients had their IDeg doses titrated using pre- Iftar (sunset-meal) and pre-Suhur (sunrise-meal) glucose values. Target glucose values were aimed to be a pre-Suhur value of 120 mg/dl, and pre-Iftar value of 130-150 mg/dl. Participants were able to adjust their bolus doses according insulin to carbohydrates ratios for each meal. IDeg was reduced initially by 15% of preRamadan dose and administered at time of Iftar. Patients were monitored using the FreeStyle Libre® flash glucose monitoring (FGM)system. Analysis of hypoglycemia were extracted from downloads and compared between different times according to eating pattern in Ramadan.

Results: At the end of Ramadan, mean BG was 176 ± 49 mg/dl and overall time spent in hypoglycemia was $5.7\% \pm 3.0\%$ of total monitoring period. The rate of hypoglycemia according to time intervals was 0%, 3%, 8%, 15% and 64% in (19:00–24:00), (24:00–04:00), (04:00–10:00), (10:00–14:00) and (14:00–19:00) respectively. Out of all hypoglycemic flashes for patients, 74% were between 60 and 69 mg/dl, 23% between 50 and 59 mg/dl, and 5% below 50mg/dl. The mean number of episodes of breaking fast was 3 (1-7). There was no significant change ($p = 0.211$) in glycemic control measured by fructosamine level between pre-Ramadan (221.7 ± 63.8 mg/dL) and end-of-Ramadan (234.8 ± 71.7 mg/dL). Insulin bolus dose had increased by 15% of the starting dose ($p = 0.03$) while basal insulin was reduced by 35±18%. No DKA or hospital admissions were reported.

Conclusion: Once daily dosing of IDeg provides safe and effective alternative for glycemic control with a significant lower risk of hypoglycemia. Hypoglycemia was encountered in the last few hours of fasting preceding Iftar time necessitating dose reduction to minimize the severity and duration of hypoglycemia. This helps adolescents with T1DM observe Ramadan in a healthy and fulfilling manner under close supervision.

P1-181**A case of prohormone convertase deficiency diagnosed with type 2 diabetes mellitus**

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Background: Prohormone convertase is an enzyme that converts many biologically inactive prohormones into biologically active peptides. Its deficiency is characterized by deficiency of variable levels in all the hormone systems. In relation to this, postprandial hypoglycemia has been reported but, a case of prohormone convertase deficiency presenting with a diagnosis Type 2 diabetes mellitus has not been previously reported.

Case presentation: A 14-year-old girl referred with complain of obesity. On the basis of her laboratory tests results, the patient was diagnosed with type 2 diabetes mellitus. Prohormone convertase deficiency was considered due to the history of resistant diarrhea in the period of infancy in her history and her rapid weight gain. Her proinsulin level at diagnosis was > 700 pmol/L (3.60-22). We noticed that c.685G> T (p.V229F) homozygous mutation in the PCSK1 gene which was not reported related with this disease before.

Conclusions: We concluded that it is important to consider the diagnosis of prohormone convertase deficiency in infants with recurrent resistant diarrhea during infancy. Our case demonstrated that if obesity starts to develop after childhood associated with recurrent serious diarrhea episodes in the history, diagnosis should be considered.

P1-182**The influence of excess iron on pancreatic beta cells**

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Objective: To establish INS-1 cell iron overload model, and study the effect on iron overload, proliferation, insulin secretion, mitochondria defect and oxidative stress change.

Methods: INS-1 cells were cultured with different concentrations (0 as control and 5, 10, 20, 40, 80, 160, 320 μ mol/L respectively) of ferric ammonium citrate (FAC). Labile iron pool (LIP) were calculated by detecting calcein-AM fluorescence in 24 h, 48 h and 72 h, when cell proliferation was accessed using CCK8. Iron overload model was established by screening for the best combination to ensure both high LIP level and cell proliferation. Reactive oxygen species (ROS) level was further detected by flow cytometer after fluorescent probe staining. The function of insulin secretion was detected by ELISA. The mitochondrial membrane potential was

detected by jc-1 kit, and the mitochondrial changes were observed by transmission electron microscopy.

Results: 1. Intracellular LIP level significantly increased in the FAC groups, and was concentration dependent. 2. The INS-1 cell proliferation was suppressed ($P<0.05$) as FAC concentration or culture time increase in the FAC groups. INS-1 iron overload model was established with conditions of 48 h given its highest LIP level and a cell viability of >50%. 3. With the increase of FAC concentration, the insulin secretion increased and then decreased, and the 160 and 320mol/L groups showed statistical difference compared with the control group ($P<0.05$). 4. ROS level significantly increased when compared with control ($P<0.05$). 5. Mitochondrial membrane potential decreased with the increase of iron concentration. The difference was statistically significant ($P<0.05$). 6. After iron overload, the mitochondria of ins-1 cells were swollen, the internal cristae was expanded, and the normal structure was lost. With the increase of FAC concentration, the mitochondrial structure was destroyed more obviously.

Conclusion: Co-culture with FAC for 48h can successfully establish the iron overload model of ins-1 cells. Iron overload can significantly damage mitochondrial structure and increase intracellular ROS level. The survival of pancreatic beta cells is sensitive to iron, even lower doses of iron can damage beta cells. The insulin secretion can be reduced when the number of beta cells is decreased to a certain extent.

P1-183

Study on the mechanism of metformin in improving PGRN-induced insulin resistance of 3T3-L1 cell

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To investigate the effect of metformin on the PERK-eIF2α pathway in PGRN - induced insulin - resistant cell model.

Methods: The 3T3-L1 Insulin-resistance cell model was constructed by dexamethasone and PGRN. Metformin was used to act on the cell model to screen out the optimal concentration group for reducing PGRN, The experiment was divided into the normal control group, dexamethasone group, and PGRN group. 4-PBA and metformin were used to act respectively. Western Blot was used to detect the expression of insulin signaling factor and PERK-eIF2α signaling factor in each group.

Results: After the action of PGRN and dexamethasone, p-Akt decreased, p-IRS-1, p-PERK, p-eIF2α increased while after the treatment with 4-PBA and metformin, p-Akt increased, p-IRS-1, p-PERK, p-eIF2α decreased. ($P<0.05$).

Conclusion: Metformin acts on the insulin resistance cell model induced by PGRN, and its effect on PERK-eIF2α pathway

and insulin pathway factor is consistent with that of endoplasmic reticulum stress inhibitor 4-PBA. It is suggested that metformin may reverse PGRN-induced insulin resistance by activating AMPK to inhibit the phosphorylation of PERK-eIF2α, an endoplasmic reticulum stress pathway.

P1-184

A case with monogenic diabetes caused by RFX6 mutation in a 14-year-old-girl

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Introduction: In previous times, diabetes mellitus in children and adolescents was usually type 1 diabetes which was caused by autoimmune beta cell destruction, but due to the increased prevalence of obesity, the incidence of type 2 diabetes was explosively increased in children and adolescents. The underlying mechanism of childhood-onset type 2 diabetes mellitus may be different to the adult-onset type 2 diabetes. It is worthwhile to find new causes of monogenic diabetes to understand the mechanism of glycemic dysregulation as well as for management of diabetes mellitus. Therefore, it is useful to conduct genetic study in children with type 2 feature.

Case: A 14-year-old-girl was diagnosed as having type 2 diabetes mellitus. Initially, she was presented with glycosuria, polydipsia, and polyuria. Initial HbA1c was 11.7%. She had no specific past medical problems. Her mother was already diagnosed as diabetes mellitus and on medication. Her weight was 66.3kg (95 percentile) and height was 148.3cm (3 percentile). Acanthosis nigricans was detected in neck and axillary areas. Blood glucose, insulin, and C-peptide were 345 mg/dL, 27.2 UIU/mL, and 8.7 ng/mL, respectively. There was neither ketonuria nor acidosis. Blood lipid profile showed 200 mg/dL of cholesterol, 45 mg/dL of HDL cholesterol, and 144 mg/dL of triglyceride. Thyroid function test showed normal. She was managed with long-acting insulin and oral hypoglycemic agent (Metformin™) and her HbA1c level was 9.3% at one year after the diagnosis. To find the candidate gene, targeted exome sequencing which included 29 genes associated with monogenic diabetes was performed. Nonsense mutation of the gene *RFX6* was found (c.2661T>A, p.Tyr887*). Her mother showed same mutation of *RFX6* gene. It was known that *RFX6* gene mutation may contribute to beta-cell dysfunction and be associated with lower fasting and stimulated gastric inhibitory polypeptide (GIP) levels.

Conclusion: It may be recommended to perform the genetic test to find the candidate gene of type 2 diabetes mellitus which developed in children and adolescents. Here we report a case with monogenic diabetes caused by *RFX6* mutation in a 14-year-old-girl.

P1-185**Endothelial and heart dysfunction in children and adolescents with type 1 diabetes**

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Background/Objectives: Type 1 diabetes (T1D) is an important risk factor for cardiovascular disease (CVD). Even if CVD become mainly manifest in adulthood, the process of atherosclerosis starts in childhood. Ultrasound is a reliable and noninvasive method for detecting early structural and functional atherosclerotic changes in arterial wall and heart. Aim of this study was to determine early ultrasound signs of atherosclerosis and of left ventricular (LV) systolic and diastolic dysfunction in children and adolescents with T1D.

Methods: Ninety-four subjects with T1D [12.3±3.53 yrs.; males 59.6%; T1D duration 5.14±3.53 years] were enrolled into the study. Carotid intima-media thickness (cIMT), systolic and diastolic function indices were determined according to standardized scanning protocol and were performed by the same investigator blinded to subjects' anthropometric (Ht, Wt, BMI, pubertal status, WC, SBP/DBP) and laboratory data (HbA1c, TC, LDL-C, HDL-C, TG).

Results: cIMT, LV systolic and diastolic function indices were all in the normal range defined for healthy population. Pubertal subjects, respect to pre-pubertal ones, had significantly higher values of cIMT (0.60±0.09 vs. 0.49±0.08 mm; p<0.001), interventricular septal end-diastole (IVSd) (7.27±1.27 vs. 6.61±1.00 mm; p=0.027), deceleration time (DT) (138.3±31.7 vs. 112.6±20.9 ms; p<0.001), and isovolumetric relaxation time (IVRT) (60.8±14.1 vs. 53.1±9.58 ms; p=0.006). Patients with DKA at T1D onset had significantly higher values of IVSd respect to subjects without DKA (7.40±1.22 vs. 6.80±1.17 mm; p=0.018). Moreover, DBP (Chi-Square=6.13; p=0.047), LV internal dimension at end-diastole (LVIDd) (Chi-Square=7.25; p=0.027), A wave peak (Chi-Square=6.11; p=0.047), and IVRT (Chi-Square=7.29; p=0.026) were significantly different according to mean HbA1c value in the last year. cIMT was higher in subjects with a worse glycemic control (HbA1c ≥9%) (Chi-Square=5.07; p=0.079) and cIMT was significantly correlated with age (R=0.51, p<0.001), WC (R=0.39, p<0.001), SBP (R=0.41, p<0.001), mean HbA1c values of the first 5 years of T1D (R=0.24, p=0.021), TG (R=0.23, p=0.029), and TG/HDL-C ratio (R=0.22, p=0.034). The multivariate regression model was statistically significant for cIMT ($R^2=0.44$, p<0.001) and identify T1D duration ($\beta=-0.23$; p=0.024) and LDL-C levels ($\beta=0.20$, p=0.031) as predictor factors.

Conclusions: cIMT were within normal range but, despite the good glycemic and lipid control, mean values were significantly higher respect to published ones in healthy and T1D children and adolescents. Moreover, LV diastolic function was slightly abnormal. Ultrasound is useful for early detection of subjects with a greater cardiovascular risk who can benefit from targeted therapeutic interventions.

P1-186**Efficacy of autologous hematopoietic stem cell transplantation in the treatment of childhood type 1 diabetes**

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Objective: To observe and analyze the efficacy and safety of autologous stem cell transplantation (AHSCT) in children with type 1 diabetes.

Methods: Twelve children were enrolled in our study who were newly diagnosed as type 1 diabetes in Children's Hospital of Fudan University from Sep. 2009 to Dec. 2011. Changes in the exogenous insulin requirement were observed and HbA1C and C peptide level were measured before and after AHSCT.

Results: After transplantation, insulin dependence was observed in 2/12 patients. Complete remission rates were 2/3, 1/2 and 1/4 after transplantation for 6, 24 and 48 months respectively. The level of HbA1c decreased after transplantation. After 3 and 6 months, HbA1c level reduced significantly compared with basal level (5.21±1.01%, 5.82±0.60% vs 11.57±0.87%, p<0.01). The significant difference still exist after 24 months. Meanwhile, the C peptide level enhanced a lot. C peptide level after 6 and 12 months increased significantly (1.47±0.83ng/ml, 1.63±0.78ng/ml vs 0.55±0.14ng/ml, p<0.01). However, no relationship was found between complete remission duration and other parameters, such as height, weight, BMI, DKA or not, HbA1c level, C peptide level before transplantation. No serious complication was observed during the whole phase.

Conclusions: Our data indicated that AHSCT has slight complication and could significantly improved β-cell function. Although AHSCT failed to cure type 1 diabetes, but it can prolong the remission period for new onset patients.

P1-187**Course of puberty and growth spurt in boys with type 1 diabetes**

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Background: Data on the course of puberty and pubertal growth in boys with Type 1 diabetes (T1D) are sparse.

Objectives: To study the course of puberty, pubertal growth and final height in boys with T1D as well as possible factors affecting these.

Methods: In this retrospective longitudinal study, 68 boys diagnosed with T1D between 1996-2009 who were pre-pubertal at diagnosis and had completed puberty served as the cohort. Collected were data on anthropometric measurements, Tanner stage, and HbA1c levels from diagnosis to final height (F-Ht). F-Ht was compared to parental height and to the data of the national health survey

Results: In the study cohort final height-SDS was lower than that at diagnosis. It was similar to parental Ht-SDS as well as to that of the national health survey ($p=0.126$). F-Ht was inversely related to average HbA1c during puberty ($R=-0.27$, $p=0.045$). Boys who presented with diabetic ketoacidosis at diagnosis were shorter than those who did not throughout the entire follow-up. Age at onset of puberty was significantly related to the age of maternal menarche ($R=0.44$, $p=0.01$) and to HbA1c levels in the year preceding puberty onset ($R=0.36$, $p=0.01$). Total pubertal growth was inversely related to HbA1c levels in the year preceding onset of puberty (average $R=-0.3$, $p=0.03$)

Conclusions: Boys with T1D diagnosed before puberty achieve final height similar to that of their parents and that of the general population. Diabetic ketoacidosis at the diagnosis is associated with diminished F-Ht. Age of pubertal onset and F-Ht are affected by genetic factors as well as by glycemic control before and during puberty. These results emphasize the importance of tight metabolic control in adolescents, to enable growth within the genetic target.

P1-188**A novel mutation in the Pancreatic duodenal homeobox-1(PDX-1) gene in a Palestinian family resulting in Neonatal Diabetes associated with congenital adrenal hyperplasia**

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Background: PDX-1 gene is involved in the early development of the pancreas and plays a major role in glucose-dependent regulation of insulin gene expression. Defects in this gene cause pancreatic agenesis, which can lead to early-onset insulin-dependent diabetes mellitus (IDDM).

Clinical Data: A 1-day-old male newborn, admitted to NICU due to antenatal diagnosis of duodenal atresia, polyhydramnios and IUGR. Laparotomy revealed duodenal web, resection was done with duodeno-duodenal anastomosis. He was noticed to have hyperglycemia since admission, C-peptide: <0.02, Insulin level <0.5, normal thyroid function tests, abdomen CT was suggestive of dorsal pancreatic agenesis. During hospitalization he showed electrolytes disturbances in form of hyponatremia and hyperkalemia, ACTH stimulation test was done and was suggestive of congenital adrenal hyperplasia. He was managed with hydrocortisone & Fludrocortisone.

Molecular Data: DNA sequencing of the PDX-1 gene for the patient revealed a novel homozygous mutation Leu166Pro in exon 2 of the PDX1 gene. Father & Mother were heterozygous for the same mutation. Functional studies are being processed.

Conclusion: Congenital absence of the pancreas is an extremely rare condition; To our knowledge, this is the first description of this disease in a Palestinian family with molecular confirmation with a unique association with congenital adrenal hyperplasia, allowing accurate genetic counseling, early diagnosis of affected kin-dreds, early therapeutic interventions and avoiding complications.

Functional studies results will allow more understanding of the condition.

P1-189**A Novel SLC2A2 mutation implicated in Fanconi Bickel syndrome and dysglycemia**

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Background: Fanconi Bickel syndrome (FBS) is a rare form of glycogen storage disease (GSD) inherited in an autosomal recessive manner and caused by mutations in the SLC2A2 gene leading to the loss of GLUT2 glucose transporter expression. The disease is considered to be rare in which a little more than 100 cases have been reported in the literature. The SLC2A2 gene encodes for GLUT2, a low affinity facilitative glucose transporter expressed in critical tissues involved in glucose homeostasis such as hepatocytes, pancreatic β -cells, and renal tubular cells. FBS is characterized by

impaired utilization of glucose and galactose, tubular nephropathy and hepatorenal glycogen accumulation. Dysfunctional and reduced expression of GLUT2 causes fasting hypoglycemia, post-prandial hyperglycemia, diabetes mellitus (DM), hepatomegaly, glucose and galactose intolerance, partial resistance to adrenaline and glucagon, rickets, and poor growth. The role of dysfunctional GLUT2 in the cause of DM is still not clearly understood.

Objective(s): 1. To describe the clinical and genetic characteristics of a new case of FBS patient associated with dysglycemia. 2. To understand the molecular basis of DM in Fanconi Bickel syndrome.

Case Report: A 22 months old Palestinian boy, born to first degree cousins, presented with severe proximal tubular dysfunction, hepatomegaly, rickets, developmental delay, and failure to thrive. Biochemical tests showed high levels of random blood glucose but low C-peptide levels. Urine analysis showed proteinuria, glycosuria, phosphaturia and aminoaciduria.

Methodology: Genomic DNA and RNA were isolated from peripheral blood samples, and analyzed by Whole Exome Sequencing (WES) and Sanger sequencing. CRISPR was used to generate the mutation.

Results: A novel homozygous nonsense mutation (c.901C>T) in the SLC2A2 gene (R301X) was found and confirmed by Sanger sequencing. To investigate the impact of this mutation, CRISPR/Cas9 system was used to substitute the nucleotide C by T at position 901. Beta cells were co-transfected by a plasmid carrying Cas9, the specific gRNA to target GLUT2 and DNA oligo donor template to specifically substitute C by T at the position 901. Edited cells carrying the specific mutation were diluted and cultured at low cell concentration to isolate single colonies and establish a Glut2 knock-out cell. The Glut2 knock-out will be used to understand the functional and structural characterization of the disease.

Conclusions: Future directions include doing the functional analysis to clearly understand the molecular mechanisms underlying the disease and develop the targeted precision therapies specifically designed for the molecular changes and associated DM and FBS syndrome.

P1-190

Periodontal disease relates to diabetes control in children and adolescents with type 1 diabetes

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Background: Obese children with and without Type 2 diabetes have periodontal disease that relates to systemic inflammation. There is limited data on periodontal disease in children with Type 1 diabetes (T1D).

Aim: We aimed to assess periodontal disease markers and its determinants in children and adolescents with T1D.

Materials and Methods: Cross-sectional study including 73 children with T1D (34 males, mean age 13.7 ± 2.6 years) were recruited consecutively from paediatric diabetes clinics at the

Women's and Children's Hospital (Adelaide, South Australia) for a comprehensive oral health assessment and collection of two gingival swabs for salivary microbiome analysis. Periodontal health parameters using plaque index, gingival index, bleeding on probe index and periodontal pocket depth were measured. Orthopantomogram and bitewing radiographs were taken. Clinical data included diabetes duration, insulin regimen, HbA1c and body size measurements.

Results: Children with T1D had mean \pm SD diabetes duration 5.7 ± 4.0 years, total daily insulin dose 0.73 ± 0.30 units/kg/day, body mass index 22.2 ± 3.9 kg/m², median [Range] HbA1c 8.2 [5.8-13.3]% and 29/73 were using continuous subcutaneous insulin infusion. None of the children had clinical background diabetic retinopathy or microalbuminuria; or were taking angiotensin converting enzyme inhibitors or statins. Four had celiac disease and 2 had hypothyroidism.

The average plaque index was 0.93 ± 0.52 , gingival index was 0.68 ± 4.3 , percentage of bleeding on probing sites $22.2 \pm 19.4\%$. The presence of periodontal disease by presence of a periodontal pocket depth greater than 3mm occurred in 37/73 (51%) of the children examined. Children with HbA1c ≥ 8.2 % [n=38] compared to those with HbA1c < 8.2% [n=35] had significantly higher markers of periodontal disease: plaque index (1.11 ± 0.5 vs 0.7 ± 0.5 , p=0.02), gingival index (0.81 ± 0.42 vs 0.55 ± 0.42 , p=0.01) and percentage of bleeding on probing sites ($29.0 \pm 20.3\%$ vs $15.0 \pm 15.6\%$, p= 0.001).

Conclusions: About one half of the children and adolescents with T1D had early periodontal disease, which was more marked with poorer metabolic control. Dental management should include routine periodontal assessment and education in children and adolescents with T1D.

Fat, Metabolism and Obesity

P1-191

Effect of Probiotics intake on obese children

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Background: Childhood obesity has been a worrisome public health issues today. Recent studies conducted in adult populations and animals have suggested beneficial effects of probiotics on obesity, while, the experience is limited in the pediatric age group and the results are conflict.

Object: The primary objective was to determine the effect of Probiotics consumption on weight change. The secondary objective was to determine the effect of the treatment on levels of inflammatory cytokines, serum lipid profile and glucose metabolism.

Methods: This randomized double-blind trial was conducted among obese children aged 6 to 14 years old. They were randomly allocated to receive probiotic capsule (containing *Bifidobacterium longum*, *Lactobacillus bulgaricus* and *Streptococcus thermophilus*) for 12 weeks. All of them treated with a reduced calorie intake

and increased physical activity. The anthropometric, inflammatory cytokines, blood lipids and fasting blood glucose, Insulin were measured at both baseline and at the end of the study.

Result:

1) A total of 54 obese children participate in the study. 30 were randomized to the probiotic group(19 boys and 11 girls, mean age 9.88 ± 1.79 years, mean BMI 25.73 ± 3.71 kg/m²) and 24 were randomized to the placebo control group(15 boys and 9 girls, mean age 9.60 ± 2.07 years, mean BMI 25.35 ± 3.57 kg/m²).

2) Compared to control group, probiotic consumption significantly reduced Body Mass Index(BMI), Inflammatory markers (interleukin-6, Lipopolysaccharide binding protein, Tumor necrosis factor α), Triglyceride, fasting blood glucose, Insulin and Homeostasis model assessment of insulin resistance(HOMA-IR) ($P < 0.05$).

Conclusion: Receiving 12 weeks probiotic supplement can improve body mass index as well as components of the inflammatory and Glycolipid metabolism. Additionally, to the best of our knowledge, this is the first study showing the effects of probiotic on Lipopolysaccharide binding protein in obese children.

proved (27,09; SD= 11,10; p<0,02) as did the number of awakenings (1,70; DE: 0,65; p=0,001) at week 8. The number of awakenings was greater in adolescents than in children at week 8 (1,95; SD=0,61; p=0,002). At 1 year follow-up, the number of awakenings decreased (p=0,006) and the total sleep time increased (p=0,006). At year 2 follow-up there was an association between weight and the number of awakenings ($r=0,36$; $p=0,0122$) and between the number of awakenings and waist circumference ($r=0,43$; $p=0,028$). The sleep efficiency improved at year 2 follow-up in comparison with baseline (2,72%, IC -3,93; -1,50, SD= 3,98; p<0,0001). There were no statistically significant differences in the sleep parameters in any phase of the study between control and intervention groups.

Conclusions: The significant change observed in the anthropometric variables which was observed at the end of intensive phase, remained throughout the follow-up. The significant improved in the sleep efficiency at year 2 follow-up in association with the tendency to decrease the number of awakenings and the increase in the total sleep time could contribute to decrease the cardiometabolic risk in children and adolescents with central obesity.

P1-192

Changes in objectively measured sleep quality after an integral intervention in patients with abdominal obesity

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Aim: To study sleep quality, using accelerometry in children and adolescents with abdominal obesity after a multidisciplinary intervention.

Patients, Material and Methods: We included 122 children and adolescents, range age: 7 to 16 years old, diagnosed with abdominal obesity (waist circumference > p90) who participated in an 8-week intervention program to lose weight, with a 2-year follow-up period. Participants were divided in 2 groups: intervention and control. The intervention group was treated with a hypocaloric Mediterranean diet and the control group followed the food guide pyramid (SENC, 2007). Throughout the intervention, all participants were encouraged to increase their physical activity by 200 minutes per week at 60-75% of their maximum heart rate. Sleep was assessed by accelerometry (wActisleep-BT, Actlife6 program) at the beginning of the study, at week 8 and at years 1 and 2. The anthropometric parameters analyzed were: weight, body mass index, hip and waist circumferences. The sleep parameters analyzed were: number of awakenings, total sleep time and the sleep efficiency. STATA 12.0 was used for the statistical analysis.

Results: The anthropometric parameters improved ($p<0,03$) both at week 8 and at year 1 and 2 follow-up. In the children group, a tendency to improve sleep quality was observed after the intensive phase. In the adolescents group total sleep time im-

P1-193

Circulating Insulin-like Growth Factor-I independently predicts blood pressure in apparently healthy children

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Background and Objectives: In adults, discordant associations exist between insulin-like growth factor-I (IGF-I) and blood pressure with scarce reports in apparently healthy children. IGF-I levels increase during puberty in parallel to calcium and phosphorus levels. In this context, our aim is to study the association between IGF-I and blood pressure in apparently healthy children, together with the interaction of the serum calcium-phosphorus product (Ca*P) in this association.

Methods: Subjects were 521 apparently healthy children (age 8.8 ± 0.1) participating in a longitudinal study of cardiovascular risk factors in Spain, of whom 158 were followed-up after 5 years. IGF-I, IGFBP-3, serum calcium and phosphorus were measured at baseline. Anthropometric [body-mass index (BMI) and waist] and cardio-metabolic [systolic (SBP) and diastolic blood pressure, pulse pressure, insulin, homeostatic model assessment of insulin resistance (HOMA-IR), HDL cholesterol and triglycerides] variables were assessed at baseline and at follow-up.

Results: IGF-I and IGF-I/IGFBP-3 molar ratio positively correlated with BMI, waist, SBP, DBP, pulse pressure, insulin, HOMA-IR and triglycerides (r from 0.198 to 0.603; all $p<0.01$). The strength of the associations with SBP increased with increasing Ca*P at baseline and at follow-up (r from 0.261 to 0.625 for IGF-I; and r from 0.174 to 0.583 for IGF-I/IGFBP-3 molar ratio). After adjust-

ing for confounding variables, IGF-I and IGF-I/IGFBP-3 molar ratio remained independently associated with SBP in children in the highest Ca²⁺P tertile, both at baseline and at follow-up (β from 0.245 to 0.381; $p<0.01$; model R² from 0.246 to 0.566).

Conclusions: Our results suggest that IGF-I is an independent predictor of SBP in apparently healthy children. This association is potentiated in children with high Ca²⁺P levels.

P1-194

Whole exome sequencing to identify causative variants in a female patient with early onset obesity and intellectual disability: a new case of Borjeson-Forsman-Lehmann syndrome

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The epidemic spread of obesity in children has triggered the commitment of scientific research, which has allowed us to understand its genetic basis; the different forms of genetic obesity share common clinical aspects, making it difficult to achieve a molecular diagnosis based only on our clinical suspicion. We report a female patient presented with neonatal hypotonia, hyperphagia and early onset excessive weight gain, strabismus and high hypermetropia. Regarding her neurodevelopment, she walked at 30 months and showed expressive language delay. The phenotype of our patient has evolved over the years with persistence of increasing obesity and onset of hepatic steatosis, hyperinsulinism and insulin resistance. PWS-AS test and array-CGH resulted normal. We performed whole-exome sequencing (WES) that disclosed a *de novo* missense mutation in *PHF6*, within the PHD-type 2 domain of the protein; X-inactivation analysis showed normal X-inactivation in blood lymphocytes. Mutations affecting the coding region of this gene or its splicing have been associated with Borjeson-Forsman-Lehmann syndrome (BFLS), an X-linked recessive disease, characterized by intellectual disability (ID), epilepsy, hypogonadism, hypometabolism, obesity. Female carriers usually not show any findings or present only mild symptoms. To date, although this condition is referred as an X-linked recessive, *de novo* aberrations in *PHF6* were reported in 12 females with a variable phenotype, characterized by ID, characteristic facial features, fingers and dental anomalies, only partially overlapping with the male phenotype. Our case, once again, underlines how the X chromosome inactivation, different in different tissues, can produce variable clinical

phenotypes related to the same condition, and that some disorders are not really transmitted as recessive. Furthermore, this situation further complicates the clinical picture of complex diseases, like early-onset genetic obesity forms. WES is a fundamental tool to identify causative variants, reducing time and costs of diagnosis and offering the opportunities for targeted management and therapy.

P1-195

Serum leptin, adiponectin and insulin-like growth factor I during infancy were associated with markers of metabolic syndrome at six years of age

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Objective: Metabolic programming occurs during early life and nutritional factors are known to have long-lasting influences on metabolic health. We investigate associations between insulin-like growth factor I (IGF-I), leptin and adiponectin during infancy and metabolic markers in the same children at six years of age.

Method: The Swedish longitudinal Halland Health and Growth birth cohort study is population-based, originally including 388 newborns 2008. The cohort has also data on essential fatty acids in serum and from maternal breast milk as well as metagenomics of gut microbiota, but is not currently presented.

From this cohort serum IGF-I, leptin and adiponectin was analyzed at birth and four months of age, and these infant data were compared to body mass index (BMI), fasting insulin and cholesterol in 188 that remained in the study at six years of age.

Results: Compared to children with normal weight (n=153), those children that were obese or overweight at six years of age (n=35) had at four months of age lower serum adiponectin ($p = 0.002$), higher serum IGF-I ($p < 0.001$) and higher serum leptin ($p = 0.04$). A lower serum IGF-I at four months correlated with a larger change in BMI from infancy to six years of age ($p < 0.001$). A significant larger increase in BMI was also seen in those six children that were born small for gestational age ($p = 0.02$), and these had a significantly higher mean \pm standard deviation fasting insulin level at 6 years of age (7.2 ± 2.1 versus 4.8 ± 2.4 , $p = 0.02$). Despite adjusting for sex, birth weight and current BMI, infant IGF-I was still associated with fasting insulin at six years of age ($p = 0.04$). Despite adjusting for sex, birth weight and current BMI, infant adiponectin was associated with fasting high-density lipoprotein cholesterol at six years of age ($p = 0.01$). Again after adjustment, infant leptin accounted for 14% ($\beta = 0.39$, $p < 0.001$) of fasting triglyceride levels at 6 years of age.

Conclusion: Serum IGF-I and adipokines at four months of age were associated with metabolic markers in the same children six years later. Despite adjusting for known influences such as fetal growth, sex and current body size there seems to be an early programming of the metabolic status by growth factors probably correlated through nutrition.

P1-196

Why are patients with obesity due to leptin receptor deficiency not sufficiently recognized? Prevalence estimation based on European allele frequencies and thoughts on the discrepancy

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Background: Biallelic loss of function (LoF) mutations in the leptin receptor gene (*LEPR*) cause a striking phenotype of early-onset severe obesity and hyperphagia. Additionally, hypogonadotropic hypogonadism, growth hormone deficiency, and/or hypothyroidism are often present. Currently, 19 European patients (all aged <30 years) are described in literature. As clinical trials investigating MC4R-agonist treatment are performed throughout Europe, identification of these patients is vital. The aim of this study was to estimate the number of LepR deficient patients in Europe.

Methods: We performed a systematic literature search and developed a list of LoF variants in *LEPR* from literature and our in-house genetic data. Subsequently, we extracted the allele frequencies from the Genome Aggregation Database (data of ~64.000 European individuals without severe paediatric disease). Through a comprehensive epidemiologic analysis, we estimated the number of individuals with homozygous or compound heterozygous known and predicted pathogenic variants in *LEPR* in Europe analogous to Ayers et al. (*JCEM* 2018;2601-12) and a conservative estimation using only known pathogenic mutations previously identified in patients.

Results: Literature research revealed that there are 75 cases published, with 42 distinct *LEPR* mutations. We add two new cases: a boy diagnosed at age 1 year with BMI 24.6 kg/m² (+4.4SD), hyperphagia, growth hormone deficiency and central hypothyroidism; and a girl with early-onset obesity and hyperphagia, diagnosed at age 11 years with a BMI of 28.5kg/m² (+3.1SD). Our conservative prevalence estimation (n=7 pathogenic variants from known patients) results in a predicted 278 (95% CI 179-378) patients with LepR deficiency in Europe, suggesting that at utmost 8% of European patients are described in literature. By using the less conservative method (n=94 variants with known or predicted pathogenicity), the number of estimated European patients is 8926 (95% CI 8039-9814).

Conclusion: We find a large gap between the estimated number of patients with LepR deficiency in Europe and those described in literature. This discrepancy suggests that the typical clinical phenotype of LepR deficiency (extreme weight gain in first years of life and often clinical signs of hypopituitarism) is not sufficiently recognized. A possible cause is lack of access to *LEPR* genetic test-

ing, which only recently became accessible. Moreover, the phenotype might not be overtly present or might resolve over time. The young age of known patients suggests that high mortality could also play a role. With promising clinical trial results of MC4R-agonist treatment in LepR deficient patients, the importance of diagnosing LepR deficiency is paramount.

P1-197

You are what you eat: preliminary evidence of associations between dietary habits and oral microbiota composition in early childhood

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Background: Oral microbiota composition and diversity differ between obese and non-obese individuals. However, the associations between lifestyle habits (implicated in the pathogenesis of obesity) and the oral microbiota remain uncertain, particularly among children.

Objective: To explore the associations between oral microbiota diversity and lifestyle habits among 8-10 year-old children.

Methods: Data stem from the baseline assessment of the QUALITY cohort, a prospective cohort study of 630 children aged 8-10 years at recruitment, with a parental history of obesity. Lifestyle habits assessed include: physical activity by 7-day accelerometry, self-reported screen time, and dietary intake by 3 non-consecutive 24h dietary recalls. Fitness was measured by VO₂peak. 16S-rRNA based microbial profiling of oral plaque samples obtained from 80 participants (40 normal weight, 40 overweight/obese) were performed to determine the diversity of the oral microbiota. Measures of diversity include Observed OTUs, Chao1, Shannon and Simpson reciprocal indices. Pearson's correlations assessed associations between diversity indices and lifestyle habits.

Results: Percent carbohydrate intake was positively correlated with all measures of diversity (Obs OTUs r=0.22, p=0.06; Chao1 r=0.23, p=0.042; Shannon r=0.19, p=0.096; Simpson reciprocal r=0.20, p=0.076). Conversely, while not reaching statistical significance, modest negative correlations between total dietary fat and saturated dietary fat consumption and measures of oral microbiota diversity were noted (r = -0.14 to -0.17 across all indices). Physical activity, fitness and screen time were not associated with oral microbiota diversity at 8-10 yr.

Conclusions: These preliminary findings suggest that dietary intake in childhood is associated with the bacterial diversity of the oral cavity.

P1-198

Correlation of serum chemerin concentrations with obesity/metabolic syndrome characteristics in pre-adolescents and adolescents

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Background: Chemerin, a protein mainly synthesized in the adipose tissue and liver, belongs to the adipokines family and is implicated in signaling for adipocyte differentiation and lipolysis. From this point of view, chemerin can exert an important role in the regulation of various pathophysiological functions, including lipogenesis and metabolism.

Objective: The aim of this study was to investigate the relationship between chemerin serum concentrations and several demographic (e.g., gestational age at birth, age, sex), anthropometric (e.g., weight, length and head circumference at birth), biochemical (e.g., serum creatinine, urea levels), bone mineral density and obesity/metabolic syndrome indices (e.g., BMI, serum glucose, triglycerides levels) in 74 pre-adolescents and adolescents 7-15 years old.

Methods: Statistical analysis was performed using R language and environment for statistical computing. Initially, Kolmogorov-Smirnov test and Shapiro-Wilk tests were used to test normality of the data, while Levene's test was used for heteroscedasticity. Correlations between continuous variables following normal distribution were assessed by Student's unpaired t-test and one-way ANOVA, whereas for categorical or ordinal variables and continuous variables not following normal distribution were assessed by Mann-Whitney U-test and Kruskal-Wallis. Post hoc tests were also applied to identify potential different groups. Chemerin data were analyzed both as continuous and as binary variables. A cut-off value of 1ng/ml (based on the distribution data) was used for the categorization. Univariate and multivariate logistic regression was further utilized when chemerin was treated as a binary variable. The predictability and discriminatory capacity of the models was assessed by receiver operator characteristic curve and its area under the curve. In all cases, statistical significance was set at the P < 0.05 level.

Results: High/low chemerin levels were found to correlate with glucose concentrations, indicating that subjects with high chemerin levels (>1ng/ml) had lower glucose concentrations. Boys with high chemerin levels had lower bone mineral density z-scores. Girls with high chemerin levels were taller, older, had higher creatinine and triglyceride levels and higher bone mineral density z-scores. Several other trends were also found relating chemerin levels with Tanner stages for breasts in girls and genitals in boys.

Conclusion: Chemerin levels were found to significantly correlate with characteristics related to obesity/metabolic syndrome in pre-adolescence and adolescence.

P1-199

Non-alcoholic fatty liver youth with obesity

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Background: Non-alcoholic fatty liver disease (NAFLD) is a highly prevalent chronic liver disease which occurs in the setting of insulin resistance and increased adiposity. It has rapidly evolved into the most common liver disease seen in the pediatric population. NAFLD can be divided into non-alcoholic fatty liver (NAFL), which denotes bland steatosis, and non-alcoholic steatohepatitis (NASH), which is marked by steatosis and lobular inflammation and hepatocellular injury. Additionally, the presence of fibrosis may indicate a more severe phenotype even in the absence of NASH. Liver biopsy should be considered for the assessment of NAFLD in children who have increased risk of NAFLD and increased liver enzymes or splenomegaly. We aimed to investigate NAFLD in youth with overweight/obesity.

Methods: We performed retrospective analyses of the clinical, laboratory, imaging and histological data of 37 children and adolescents with overweight/obesity, followed at our Institution, who underwent liver biopsy between 2006 and 2017. Participants underwent liver biopsy during bariatric surgery (n=22) or percutaneously (n=15). The presence of co-morbidities such as increased liver enzymes (ALT≥80; AST/ALT>1); splenomegaly, hypertension (BP≥130x80mmHg/use of anti-hypertensive medications), Type 2 diabetes (T2D; 2h-OGTT≥200mg/dL), impaired glucose tolerance (IGT; 140<2hOGTT<200mg/dL), insulin resistance (HOMA-IR≥2.5), and dyslipidemia (TC≥200 or non-LDL-C>135 or HDL-C<40 for boys and <45 for girls or TG>130 mg/dL) were computed. Participants with other causes of chronic liver diseases were excluded. Results were based on the NASPGHAN criteria.

Results: The mean age of the participants was 15.8 years (± 3.29) and 65% were boys. Mean BMI was 39.3kg/m² and all participants had a waist circumference $\geq 90^{\text{th}}$ percentile. While 73% had liver steatosis diagnosed by the ultrasound, none had splenomegaly. Although only 4 participants had increased liver enzymes, NAFLD was diagnosed in 33 (89%) patients. The histological evaluation showed liver steatosis in 89% of the samples (30.3% stage 1; 39.4% stage 2; 30.3% stage 3). From those 33 participants, 63.3% also presented with steatohepatitis (76.2% stage 1; 9.5% stage 2; 14.3% stage 3) and 63.6% with fibrosis. Moreover, NASH was diagnosed in 24 (72.7%) of those participants. T2D, IGT, insulin resistance, hypertension and dyslipidemia were present in 8.1%, 5.4%, 91.9%, 59.5%, 73% participants, respectively.

Conclusion: NAFLD was highly prevalent among youth with overweight/obesity. Since NAFLD can result in progressive fibrosis and lead to end-stage liver disease, we should consider other screening tests, aside from increased liver enzymes and splenomegaly, in order to make early diagnosis in this population.

P1-200

Ferritin, an indicator for inflammation or iron storage in obese children?

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Ferritin is a widely used iron storage indicator. At the same time, it is also viewed as an indicator of inflammation. Chronic low-grade inflammation in obese individual, especially in the one with metabolic disorders, related to comorbidities and poor prognosis. Both hyperglycemia and iron overload can induce inflammation and result in vascular endothelial dysfunction. To study the role of ferritin in obese children and its impact on artery and liver, the present study investigated 196 obese children for the correlations of ferritin level and intima-media thickness (IMT), liver function and fibrosis index, as well as hemoglobin, blood pressure, blood lipids, blood glucose in OGTT test, and inflammation indicators.

IMT was detected by high-resolution B-mode ultrasonography of the right and left carotid arteries. Serum markers of hepatic fibrosis: HA, CIV, P_cIII and LN were measured using the ELISA kits. Statistical analysis was performed using SPSS 16.0. Indicators were log transformed or reciprocal transformed to get a normalized contribution and then were analyzed by Pearson correlation coefficient.

Obese children have significantly higher ferritin levels compared to control. Ferritin level in obese children correlated to waist/height ratio but not BMI. After controlled for waist/height ratio, ferritin level also correlated to hemoglobin, blood pressure, LDL, and glucose levels during the OGTT. Ferritin level does not correlate with other indicator of acute inflammation, including white blood cell counts, neutrophil percentile and platelet counts. However, it correlated to bile acids, an indicator for hepatic inflammation, as well as liver fibrosis markers type IV collagen (CIV) and procollagen type III (P_cIII). For IMT, it correlated to BMI but not ferritin.

In obese children we studied, ferritin level is an indicator for iron storage. At the same time, it related to central obesity and also chronic liver inflammation, as well as metabolic syndrome components, including hypertension, high LDL and impaired glucose tolerance. However, ferritin level may not be an indicator for artery change and systemic inflammation.

P1-201

Serum Kisspeptin in Obese Children and Its Relation to Glucose Metabolism

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Background: The neuropeptide kisspeptin has recently been demonstrated to play a role in regulating energy balance and glucose metabolism. Previous studies showed a positive effect of serum kisspeptin in relation to glucose metabolism. These included negative association between serum kisspeptin and body mass index (BMI), homeostatic model assessment of insulin resistance (HOMA-IR) and plasma insulin. However, some studies reported conflicting results. Data on serum kisspeptin in obese children are limited.

Objective: To determine serum kisspeptin in obese children and its relation to glucose metabolism

Methods: There were 133 obese children included. All children underwent an oral glucose tolerance test (OGTT) and had their fasting serum kisspeptin levels measured. Insulin secretion (HOMA- β and insulinogenic index) and insulin sensitivity (whole body insulin sensitivity index and HOMA-IR) indices were assessed using serum glucose and insulin levels derived during the OGTT. Serum kisspeptin in relation to glucose metabolism was analyzed.

Results: Median (IQR) age of enrolled children was 11.8 (10.8, 13.5) years and 57 of them (43%) were males. There were 18 (14%), 83 (62%) and 32 (24%) patients with normal glucose tolerance (NGT), hyperinsulinemia with normal glucose (HI) and abnormal glucose tolerance (AGT), respectively. BMI Z-scores were not different among these 3 groups. Males had higher serum kisspeptin levels than females [68 (37, 83) vs. 48 (25, 73) pg/mL, $p = 0.043$]. Patients with Tanner stages II & III had higher serum kisspeptin levels than those with Tanner stage I [63 (37, 79) vs. 15 (9, 73) pg/mL, $p = 0.049$]. Serum kisspeptin levels were not different among the 3 groups of glucose metabolism [NGT: 67 (32, 83), HI: 48 (27, 78) and AGT: 69 (35, 80) pg/mL, $p = 0.538$]. Serum kisspeptin levels were also not different among the different BMI Z-score tertiles. There were no correlations between serum kisspeptin levels and insulin secretion or insulin sensitivity indices in all children. However, after adjustment for sex and puberty, serum kisspeptin level was negatively associated with fasting plasma glucose (FPG) in the HI group ($\beta = -1.487$, $p = 0.006$).

Conclusion: Serum kisspeptin levels were not different among different glucose metabolism categories. Negative correlation between serum kisspeptin and FPG was only found in the HI group.

P1-202**Visceral adiposity index as a marker of metabolic risk in survivors of paediatric hematopoietic stem cell transplantation after chemotherapy-only conditioning**

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Background: Hematopoietic stem cell transplantation (HSCT) recipients exhibit excess adiposity that may result in an increased metabolic risk. Studies have shown that BMI is a poor predictor of body fatness in pediatric HSCT survivors population where diminished lean mass has been documented. The visceral adiposity index (VAI) has recently been proposed as a predictor of cardio-metabolic risk in both adults and children. However, the predictive value of this index in metabolic risk assessment has not been studied in survivors of childhood TCSH. Therefore, we aimed to estimate the potential relationship between VAI, markers of insulin resistance (HOMA index) and body adiposity measured by dual-energy x-ray absorptiometry (DXA) in a cohort of pediatric TCSH survivors after chemotherapy-only conditioning.

Material and Method: Anthropometric measurements and metabolic/hormonal profile were obtained from 28 paediatric HSCT survivors that were not exposed to TBI conditioning. DXA was performed to measure total body fat and android/gynoid (A/G) ratio in 21 subjects.

Results: Our study showed a statistically significant correlation between VAI and HOMA index ($r^2=0.384$, $p=0.001$) and serum glucose level ($r^2=0.140$, $p=0.046$), respectively, in survivors of paediatric HSCT, but we found no association between VAI and total body fat or A/G ratio in our patients.

Conclusion: Although VAI correlated with serum glucose level and HOMA index in our group of survivors of paediatric HSCT who underwent chemotherapy-only conditioning, we found no association between VAI and densitometric parameters of adiposity. Therefore, we suggest that VAI should be used with caution in this population to predict the metabolic risk.

P1-203**Serum nonylphenol and obesity in children and adolescents**

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Background: Experimental models suggest that exposure to low dose nonylphenol could induce adiposity and promote adipocyte differentiation in mice. However, studies on the effect of nonylphenol exposure to human obesity have not been adequately studied.

Objective: We investigated the associations of serum nonylphenol concentration with adiposity measures in Korean children and adolescents.

Methods: A total of 204 children and adolescents, aged 6 to 14 years old (105 overweight-to-obese subjects and 99 controls), were recruited. Anthropometric indices including body mass index (BMI) and body fat mass (kg) were determined. The serum concentrations of nonylphenol were measured using GC-MS SIM mode. Generalized linear model procedures were used to calculate the adjusted least square geometric mean (LSGM), after controlling for physical activity, daily calorie intake, household income, birth weight, and gestational age. The logistic regression model was used to determine the adjusted [odds ratios (OR), 95% confidence intervals (CI)] for overweight and obesity.

Results: Serum nonylphenol concentrations were detected among 92.6% of subjects, and the geometric mean (95% CI) of serum nonylphenol was 2.54 (2.26-2.87) ng/mL. As the elevation of nonylphenol quartile values, adjusted mean values of obesity indices including weight, BMI percentile, and body fat mass significantly increased (P -for-trend <0.05). After adjusting for covariates, the subjects in the highest nonylphenol quartile showed a significantly increased OR (95% CI) for obesity compared with those in the lowest nonylphenol quartile [2.47 (1.03-5.92), P -for-trend <0.023].

Conclusions: We demonstrated a positive association between serum nonylphenol and obesity in girls. Longitudinal studies with larger sample sizes are needed to confirm our results.

Fetal, Neonatal Endocrinology and Metabolism (to Include Hypoglycaemia)

P1-204**Risk factors for brain injury after transient or persistent hyperinsulinemic hypoglycemia in neonates**

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Background: Aim of this study was to identify possible explanations why despite improved treatment options brain damage still occurs in neonates with transient or persistent hyperinsulinism. This study might serve as a basis for future research to improve the management of neonatal hypoglycemia reducing brain injury in these children.

Material and Methods: A retrospective medical chart review was conducted at the University Children's Hospital Duesseldorf, Germany. Out of 115 children with transient neonatal hyperinsulinism or persistent congenital hyperinsulinism (CHI) n=11 patients with hypoglycemic brain damage were identified. Data was

analyzed in terms of most likely etiologic hypoglycemic episodes and thereafter the associated cause of brain damage was investigated.

Results: In our cohort of 11 patients, 8 had neurodevelopmental delay, one of them severe. 7 had epilepsy, 3 had impaired vision and one patient had cerebral palsy. In 7 patients, magnetic resonance (MR) brain imaging showed signs of hypoglycemic brain injury. Remarkably, three children had transient hyperinsulinism achieving remission between 3 weeks to 3 months of life. The remaining 8 patients suffered from persistent CHI. Only 2 patients had risk factors for neonatal hypoglycemia and they both had persistent CHI. All patients had very low blood glucose levels <1,4 mmol/L (<25mg/dl; range 0,1-1,2 mmol/L; median 0,7 mmol/L) in at least one measurement. In 8 patients, the lowest known blood glucose concentration was recorded in the initial glucose control. All patients had symptomatic hypoglycemia and 8 patients had at least one episode of hypoglycemic seizure. In 7 patients, a delay of several hours up to 2 months was observed between first clinical symptoms, first blood glucose control and achieving appropriate glycemic stabilization.

Conclusion: Brain damage particularly occurred in newborns without risk factors for postnatal hypoglycemia as for these newborns blood glucose screenings are not standard procedure. Brain damage in transient hyperinsulinemic hypoglycemia was a frequent finding in our cohort. Inferior neurological outcome was notably associated with a delay between first clinical symptoms, diagnosis and initiation of adequate treatment. Additionally, hypoglycemic seizures and low blood glucose levels <1,4 mmol/L (<25mg/dl) were prevalent in those with brain damage. Further research is needed to improve early identification of patients with high risk for brain damage within the large group of neonates with physiological postnatal hypoglycemia.

P1-205

Central Hypoventilation Syndrome and Hyperinsulinaemic Hypoglycaemia

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Objectives: Congenital central hypoventilation syndrome (CCHS) is a rare autosomal dominant condition due to mutations in the transcription factor *PHOX2B*. It is characterized by alveolar hypoventilation with symptoms of autonomic nervous system dysfunction and both hyperglycemia as well as hyperinsulinaemic hypoglycaemia (HH) have been reported. Although the mechanism is unclear, autonomic dysfunction may underlie this dysregulation of glucose homeostasis.

Aim: To highlight the phenotype and treatment outcome of HH in children with CCHS.

Methods: We report three children diagnosed with CCHS and HH and the challenges of their management.

Results: All cases were term infants diagnosed with CCHS in the neonatal period and were found to have mutations in *PHOX2B* of which two were heterozygous for polyalanine repeat expansions (20/27). They presented with HH in infancy (range 30-80 days of life) with fasting hypoglycemia; one case also demonstrated episodic post-prandial hypoglycemia. All responded to diazoxide (ranging 5-11.3mg/kg/day), although the case with post-prandial hypoglycemia also required overnight gastrostomy feeds. Two cases remain on diazoxide at 1.1 and 2.7 years, while a third case was gradually weaned off by 5.5 years. All three cases required long-term ventilation via tracheostomy had other characteristics of CCHS (Hirschsprung disease, autoimmunity dysfunction) as well as other features (tracheomalacia, omphalocele, seizures).

Conclusion: Dysregulated glucose homeostasis may be an under-recognised in CCHS. Episodes of hypoglycemia in children with CCHS could present either in response to fasting or postprandially. In contrast to a recent report, our cases of CCHS-associated HH exhibited predominantly fasting hypoglycemia, which could be related to the severity of their CCHS based on mutation status (or maybe directly related to mutation). These children must be monitored closely for symptoms of hypoglycemia and investigated for HH, including for post-prandial hypoglycemia if any concerns. Our case series highlights that diazoxide can be effective treatment but sometimes-dietary intervention might be necessary.

P1-206

Unusual congenital hyperinsulinism case in a patient with a pathogenic GCK mutation

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Dominant activating mutations in *GCK* gene are known to be the cause of congenital hyperinsulinism (CHI). Patients with *GCK* mutations can have a wide range of clinical presentations, varying from asymptomatic adult onset hypoglycemia to medically unresponsive severe neonatal onset HI. Overall, 5 of 214 (2.3%) patients diagnosed with HI over the last 10 years in Russia were found to carry pathogenic variants of *GCK* gene. Only 2 of these 5 patients showed response to high doses of Diazoxide (14.4 and 20 mg/kg/day), whereas others were found to be medically unresponsive. Here we report a severe GCK-HI case which required pancreatectomy. The female patient with normal birth weight and unremarkable neonatal period had her first episode of hypoglycemic seizures at the age of 14 months after weaning off nighttime feeds. At the age of 16 months the girl was admitted to Endocrinology Research Centre (Moscow, Russia), where persistent hyperinsulinemic hypoglycemia was revealed. Interestingly, the patient had normal neurological status. However, the

girl had poor response to 20 mg/kg/day Diazoxide and 18 µg/kg/day Octreotide. As the condition deteriorated and the patient got more frequent hypoglycemic episodes followed by drowsiness, stable euglycemia was achieved at glucose infusion rate as high as 19 mg/kg/min. Yet it caused anorexia and dramatic weight gain. A continuous subcutaneous glucagon infusion attempt has failed. Genetic analysis using NGS technology has revealed a mutation in GCK gene NM_000162.4: c.1361_1363dupCGG CI093751 in 11% of reads in the blood sample. Direct sequencing has confirmed the presence of mosaicism. Considering persistent hypoglycemia, high glucose infusion rate and severity of the mutation, the patient underwent near-total pancreatectomy which led to a transient normoglycemia. A few weeks after the surgery the persistent hypoglycemic episodes reoccurred. Low glucose diet with fructose intake and 12 mg/kg/day Diazoxide did not improve the condition. Partial response was achieved on 10 µg/kg/day Octreotide in combination with Nifedepine. Continuous flash glucose monitoring (FreeStyle Libre) appeared quite accurate and helpful in this case. A neurologic examination at the age of 21 months showed normal neurodevelopment with no signs of hypoglycemic brain injury. In summary, near-total pancreatectomy led to some improvement, although did not completely cure the patient. The necessity of near-total pancreatectomy in GCK-HI patients is debatable. Activating mutations of the GCK gene, which is also expressed in the brain, may possibly have some protective effects by keeping the neuronal cells active even during hypoglycemia.

P1-207

Clinical characteristics and long term follow up of 17 patients with permanent neonatal diabetes due to PTF1A distal enhancer mutations

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Background: Pancreas transcription factor-1 alpha (PTF1A), encoded by the PTF1A gene, is a beta helix loop(bHLH) protein which involved in the development of the pancreas and cerebellar neurogenesis. Although mutations of PTF1A cause permanent neonatal diabetes(PNDM), pancreas agenesis and cerebellar

agenesis, PTF1A enhancer mutations reported causing PNDM and isolated pancreas agenesis. In the present study, we evaluate the phenotype-genotype characteristics and long-term follow up of 17 patients with PNDM and isolated pancreas agenesis due to PTF1A distal enhancer mutation.

Patients and Method: NDM was defined as diabetes presented within the first 6 months of life. Presenting clinical and biochemical characteristics were reviewed from the hospital files. Molecular genetic analysis was performed for all patients and parents. The latest growth, developmental milestones and metabolic characteristics were re-evaluated.

Results: Presenting and follow-up characteristics are summarized in Table 1. Majority of cases had severe IUGR and birth weight was negatively correlated with gestational age($r=0.827; p=0.000$). All patients had clinical signs of exocrine pancreas insufficiency and pancreas agenesis/hypoplasia in imaging. Low faecal elastase was measured in 8 out of 9 patients. Insulin therapy and pancreas enzyme replacement were introduced to all patients. A transient, but markedly elevated ferritin level was detected in all patients who ferritin levels had been measured at the neonatal period. In the molecular genetics analysis, the most common mutation was PTF1A distal enhancer g.23508437A>G which was detected in 12 cases. PTF1A distal enhancer g.23508363A>G and g.23508365A>G in 2 cases and g.23508336G>T in a single case.

Conclusion: In this series of 17 cases with PNDM due to homozygous distal enhancer PTF1A mutations, severe IUGR, isolated pancreas agenesis/hypoplasia and exocrine pancreas insufficiency in all cases suggested a good phenotype-genotype correlation. Although was not measured in all subjects, markedly elevated ferritin level and its role in the phenotype of patients remain unknown and require to be further elucidated. Although all were replaced using pancreas enzyme, majority of cases failed to catch-up growth. This can be attributed to poor compliance, but, requires further investigations to clarify the exact mechanism.

Table 1. Characteristics of cases

	Median	Range
Age of diagnosis (day)	6.5	1-60
Gestational age (week)	36	28-40
Birth weight(SDS)	-3.1	-6.67-0.24
Blood glucose(mg/dl)	406	242-800
C-peptid (ng/ml)	0.1	0.01-0.5
Current age(months)	39.5	8-115
Ferritin (mg/dl)	1562	451-2000
Latest height (SDS)	-2.52	-4.17-(-0.99)
Current insulin dose (U/kg/day)	0.8	0.5-1.0
Latest HbA1c (%)	9.9	8.0-12.1

P1-208**Transient gonadal activation and infant growth velocity**

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Background: Hypothalamic-pituitary-gonadal axis is activated during the first 6 months of life, called as mini-puberty in which reproductive hormone levels may reach to adult levels. Although, our understanding of the pathophysiology of sex steroids interaction with growth in puberty is increasing, very little is known about the relationship between sex steroids and growth at this period of life.

Material and Methods: 142 (67 girls, 75 boys) healthy appropriate-for-gestational age neonates were included. Insulin-like growth factor 1 (IGF-1), insulin-like growth factor 3 (IGFBP-3), luteinizing hormone (LH), follicle stimulating hormone (FSH), total testosterone (TT) and estradiol (E2) levels were measured at postnatal 2nd month of life. In all cases height and weight were measured at the 1st, 2nd, 4th, 6th, 9th and 12th months of age. GV was monitored and compared with sex steroids and growth factors.

Results: The mean LH and TT levels were significantly higher in boys than girls ($p = 0.001$). In girls, the mean FSH level was significantly higher than in boys ($p = 0.001$). There was no statistically significant difference between the mean E2, IGF-1 and IGFBP-3 levels in boys and girls ($p > 0.05$). The GV was significantly faster from birth to 6 months of age in boys than in girls ($p < 0.05$). The highest GV was observed at 1 and 2 months of age, simultaneously with the peak of postnatal gonadal activation. There was a positive correlation between GV and TT in both sexes ($p < 0.05$).

Conclusion: These results may provide a new perspective on the effect of transient gonadal activation on infant growth velocity.

Key words: mini-puberty, testosterone, estradiol, IGF-1, growth velocity

P1-209**Urogenital abnormalities in children conceived by assisted reproductive technologies**

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Background: According to recent European and Russian monitoring hypospadias and cryptorchidism are the most frequent malformations of the urogenital system in children in the general population. Currently there is a lack of information about

the impact of assisted reproductive technologies (ART) on the development of congenital malformations, including the urogenital system, although the presence of this abnormality could lead to male reproductive disorders.

Aims: To evaluate the frequency and structure of congenital malformations of the urogenital system in children conceived by ART.

Materials and Methods: During the period from 2015 to 2018 we analyzed the data of 100 children conceived by ART. (59 children from singleton pregnancies (group 1), and 49 children from multiple pregnancies (group 2)). In group 1 there were 34 (57.6%) boys; group 2 - 19 (46.3%) boys respectively. We analyzed anamnesis of life, family history, and congenital malformations of the urogenital system.

Results: The frequency of congenital malformations of the urogenital system in group 1 was 16.9% of cases; in group 2 - 21.0% of cases, they were represented by: hydronephrosis, renal asymmetry, incomplete doubling of the kidney, hypospadias, cryptorchidism. In group 1, cryptorchidism was diagnosed in 5.9% of cases; in group 2 - 21.0%, respectively. In group 1, hypospadias was diagnosed in 5.9% of cases; in group 2 this pathology was not registered. At the same time, 75% of boys had low birth weight (< 2500 g). The average age of mothers in group 1 was 33.4 ± 1.6 ; in group 2 - 34.2 ± 1.4 years; in the Russian Federation - 28.4 ± 1.3 years, ($p < 0.05$). In 62% of cases there were patients with burdened obstetric and gynecological anamnesis.

Conclusions: The frequency of urogenital abnormalities in children conceived by ART doesn't exceed the population values. It is not associated with technology of ART, but it is induced by such factors as older age and the health of the mother, burdened obstetric and gynecological anamnesis, low birth weight.

P1-210**Subcutaneous fat necrosis of the newborn: A systematic review of the literature**

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Background: Subcutaneous fat necrosis of the Newborn (SCFN) is a rare disease occurring in the first days of life. Characteristically the infants show hard nodules in subcutaneous tissue, purple or erythematous in color and appear on the upper back, cheeks, buttocks and limbs. In most cases SCFN is a self-limiting disease, as the nodules disappear in up to 6 months. A severe complication associated with SCFN is hypercalcemia. Pathophysiological mechanisms causing SCFN or associated hypercalcemia are not fully understood yet.

Objective: We aimed to identify risk factors for SCFN or associated hypercalcemia and to better understand pathophysiological mechanisms.

Methods: A systematic literature research following the PRISMA-Statement including the six biggest databases for medical research has been used to identify all published case reports of SCFN. N=206 publications have been identified containing n=320

case reports. All cases have been classified into four subgroups (depending on the given serum-calcium-level): hypercalcemia, normocalcemia, hypocalcemia or no information given. Reported maternal factors, birth characteristics, details about SCFN, diagnostics, therapy and long-term observations have been extracted from publications.

Results: This is the first systematic literature research that summed up all published cases of SCFN from 1948 up to 2018. Information about serum calcium level was given in 64.3% of the cases. From those, the majority showed hypercalcemia (70.5%) (normocalcemia: 25.1%, hypocalcemia: 4.3%). 89.3% of newborns with hypercalcemia showed suppressed levels of the parathormone. We identified, that maternal gestational diabetes, maternal hypertensive diseases during pregnancy, macrosomia (>4000g), asphyxia and therapeutic hypothermia are risk factors for SCFN. Histological findings showed a granulomatous inflammation in 98% of cases.

Discussion: We identified that maternal, birth characteristics and therapeutic measures are probably risk factors for SCFN. These risk factors should be taken into account by the practically active paediatricians. Hypoxic cell damage is thought to be the cause of subcutaneous fat necrosis in patients with SCFN. The majority of patients with SCFN develop hypercalcemia. It is assumed that granulomatous inflammation in patients with SCFN is causing a lack of the negative feedback mechanism of the enzyme 1- α hydroxylase. As a result of this missing negative feedback mechanism vitamin D is overproduced. This causes an increased absorption of calcium via the intestine and consequently hypercalcemia. Hypercalcemia seems to be independent from parathormone levels in affected newborns.

P1-211

Characteristics of children with Kabuki syndrome and hyperinsulinemic hypoglycemia

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Background: Kabuki syndrome (KS) is a rare multiple congenital malformation and intellectual disability syndrome. KS is caused by pathogenic variants in the genes *KMT2D* or *KDM6A*. In 0.3-4% of patients, KS is reported to be associated with hyperinsulinemic hypoglycemia. The objective of this study was to characterize the clinical, biochemical and molecular data of children with KS and hyperinsulinemic hypoglycemia.

Methods: Clinical, biochemical and molecular data from 5 children with KS and hyperinsulinemic hypoglycemia from three centres were retrospectively analysed.

Results: 5 female patients were identified with 5 different pathogenic variants in *KDM6A* (n = 3) and *KMT2D* (n = 2). All of them presented hyperinsulinemic hypoglycemia at day one of life and showed good response to treatment with diazoxide. The children were diagnosed with KS between the age of 10 months and 9 years. Typical clinical features of KS were seen in all patients but were of great variety, including dysmorphic facial features (n=5), cardiac anomalies (n=4), feeding difficulties with failure to thrive (n=4), and neurological symptoms such as afebrile seizures, muscle hypotonia and developmental delay (n=4).

Conclusion: In our study all children were diagnosed with hyperinsulinemic hypoglycemia in the first days of life, however, it took months to years to diagnose the KS. The predominance of female gender and *KDM6A*-related KS in our small cohort surprises, however, existing literature does not show similar findings. To facilitate the early identification of KS associated problems and to improve the treatment of affected patients with KS, KS should be considered in children with hyperinsulinemic hypoglycemia especially if there are other extrapancreatic/syndromic features.

GH and IGFs

P1-212

Hypoglycaemia adverse events in SPIGFD: association with patient diagnosis, age, time-course and dosage of mecabolin: 10-year data from the European Increlex® Growth Forum Database in Europe (EU-IGFD)

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Background: In Europe, Increlex® (mecabolin) is approved for treatment of growth failure in children with severe primary insulin-like growth factor-1 deficiency (SPIGFD). We present 10-year data (up to October 2018) from the European Increlex® Growth Forum Database (EU-IGFD) registry (NCT00903110) on the frequency, predictive factors, and the potential impact of hypoglycaemia on efficacy outcomes.

Methods: This is an ongoing, multicentre, open-label, observational study monitoring the safety and efficacy of mecabolin in children in clinical practice. Logistic regression analysis was performed to identify predictive factors for hypoglycaemia.

Results: 280 patients were enrolled (safety population, 272 patients; 23 [8.5%] with a previous history of hypoglycaemia). Sixty-four (23.5%) patients experienced at least one hypoglycaemia

adverse event (AE; 113 events: 57 verified, 44 suspected, 12 unspecified). Twelve serious hypoglycaemia events occurred in 7 (2.6%) patients. AEs led to withdrawal of 15 (5.5%) patients (3 [1.1%] with hypoglycaemia and 2 [0.7%] with hypoglycaemic unconsciousness). Baseline characteristics of patients who subsequently experienced hypoglycaemia included a lower mean age at first mecasermin injection (8.6 years versus 9.7 years in patients not experiencing hypoglycaemia), more frequent diagnosis of Laron syndrome (31.3% versus 11.1%), and a history of hypoglycaemia events (20.3% versus 4.8%). Laron syndrome and history of hypoglycaemia were found to be predictors for hypoglycaemia (odds ratio [OR] 0.33 [95% confidence interval (CI) 0.16; 0.68], p=0.003 and OR 0.26 [95% CI. 0.10; 0.65], p=0.004, respectively; multivariate analysis). Mean first year mecasermin dose (\leq 100 μ g/kg BID versus >100 μ g/kg BID) was not associated with time to hypoglycaemia (Gehan test: p=0.554). The mean change in height standard deviation score (SDS) from baseline over the first 6 years of mecasermin treatment was similar between patients who did or did not experience hypoglycaemia: changes from baseline at 1, 3 and 6 years were 0.35 (95% CI. 0.21; 0.49), 0.79 (95% CI. 0.53; 1.05) and 0.95 (95% CI. 0.25; 1.66), and 0.33 (95% CI. 0.26; 0.40), 0.78 (95% CI. 0.62; 0.94) and 0.96 (95% CI. 0.67; 1.24), respectively.

Conclusions: Mecasermin may have hypoglycaemic effects. Special attention should be paid to young children, children with a history of hypoglycaemia and those with Laron syndrome. Hypoglycaemia had no impact on the effectiveness of mecasermin in the real-life setting.

P1-213

Determinants of final height in patients born small for gestational age treated with recombinant growth hormone

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Introduction: About 15% of children born small for gestational age (SGA) do not reach final height within normal range. Recombinant human growth Hormone (rhGH) has shown to be effective in catching up growth velocity and height in children born SGA. The objective of our study is to identify the predictive factors of final height in children born SGA treated with rhGH.

Materials and Methods: Monocentric, retrospective study in a tertiary pediatric endocrinology referral center. We included all patients older than 16 years, born SGA defined as birth length or weight <10th centile and treated with rhGH for more than one year. Patients treated with GnRH analogues (GnRHa) were included. Patients treated with aromatase inhibitors were excluded.

Results: 255 patients were included [98 boys, 157 girls]. 120 patients received GnRH analogues for precocious or advanced puberty and advanced bone maturation. They had an average birth length of -2.0 \pm 0.7 SD and birth weight of -1.6 \pm 1.0 SD. Upon 4.5 \pm 2.8 years of rhGH treatment, height increased from -2.2 \pm 0.9 to a normal height of -1.5 \pm 0.9 SD. The target height of this population was -0.8 \pm 0.8 SD.

Our multivariate analysis identified 8 factors that predict 46 % of the final height including SGA causes (R^2 =10%, p <0.0001), treatment with GnRHa > 2 years (R^2 =0.1%, p=0.006), birth length (p<0.02, R^2 =4%), height at start of rhGH (R^2 =5%, p<0.0001), IGF1 at start of rhGH treatment (R^2 =8%, p=0.0002), growth velocity during the first year of treatment (R^2 =8%, p=0.0002), age at onset of puberty (R^2 =5%; p<0.0001) and height at onset of puberty; (R^2 =4%, p=0.0007).

Furthermore, the better response to rhGH was associated to the absence of chromosomal abnormalities or bone malformations (p=0.0003), to mother's height -height between -1 SD and 0 SD (p= 0.02), to a great growth velocity at one year of treatment (OR = 1.3 [1.1-1.6], p=0.004), to an extended time on treatment (OR = 1.6 [1.3-1.9], p<0.0001) to a low IGF1 (OR=0.4 [0.2-0.6], p<0.0001), to a late pubertal development, or to short stature associated to puberty (OR = 1.9 [1.4-2.5], p<0.0001; OR = 0.6 [0.4-0.9],p= 0.03).

Conclusion: In this large cohort of patients who achieved their growth we were able to identify several factors influencing the final height and the response to growth hormone therapy in children born SGA. This will likely help the management of rhGH in the future for this specific target population.

P1-214

The European Increlex® Growth Forum Database (EU-IGFD) registry: do treatment practices differ between European countries?

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Background: In the European Union, Increlex® (mecasermin) is approved for the treatment of growth failure in children with severe primary insulin-like growth factor-1 deficiency (SPIGFD).

Methods: The European Increlex® Growth Forum Database (EU-IGFD) registry (NCT00903110) is an ongoing, multicentre, open-label, observational study monitoring the safety and efficacy of mecasermin in children in the clinical practice setting. Here we present baseline characteristics and exposure data for each participating country.

Results: As of 9 October 2018, 280 patients were screened from 10 countries, and recruitment as a proportion of the study population was highest in Germany and France: Germany (31.4%, n=88), France (23.6%, n=66), Spain (12.1%, n=34), UK (11.1%, n=31), Italy (10.4%, n=29), Poland (5%, n=14) and 'Other' countries (Sweden, Austria, Belgium and the Netherlands; 6.4%, n=18). The most frequent diagnosis was SPIGFD (244/280 patients [87.1%]; less frequent in France [68.2%] and Spain [73.5%] than Germany [97.7%] and UK [100%]). Laron syndrome was present in more patients in UK (35.5%) and Italy (34.5%) than in France (6.1%), Germany (3.4%) and Poland (0%). Mean age at first mecasermin intake was similar between countries (range: 8.59 \pm 4.36 years [Spain] to 9.87

± 3.65 years [Germany]). Mean height standard deviation score (SDS) $\pm SD$ at first mecabolin intake was lowest in the UK (-4.75 ± 1.02) and highest in 'Other' countries (-3.15 ± 1.00). Patients from Poland and Germany were less likely to have received previous growth therapy (100% and 79.5% naïve patients, respectively, vs. 60.6%, 58.8%, 64.5%, 56.0% and 55.6% in France, Spain, UK, Italy and 'Other' countries, respectively), and treatment-naïve prepubertal status varied between countries (from 91.7% in Poland to 41.7% in Italy). Therapy was discontinued because adult height was achieved in 5.9%, 23.1%, 31.7%, 36.4%, 38.9%, 40.0% and 44.4% in France, Spain, Germany, UK, Italy, Poland and 'Other' countries, respectively. The median dose of mecabolin at baseline was 40 µg/kg/BID in all countries. Median dose was titrated up to 120 µg/kg/BID after 12 months in Germany and France, but was more slowly titrated in other countries. Median (95% CI) treatment duration was longest in Poland (5.28 [2.37, 7.21] years) and shortest in France (1.92 [1.21, 2.46] years).

Conclusions: Aetiology, previous growth therapy, treatment duration, and titration rates of the mecabolin dose varied across European countries. International collaboration is needed to ensure a consistent approach to the identification and management of rare growth diseases such as SPGFD.

were $>2SD$ below age/sex specific mean value. In view of results suggesting relative resistance to GH, high-dose GH (70-75mcg/kg/d subcut.) was started. Pre-GH height velocities were 3.7 (Pt-A) and 4.5 (Pt-B) cm/year. GH dose was adjusted to sustain serum IGF1 levels towards the upper end of reference range for age. Annualized height velocities for first, second and third year on GH treatment were 7.0, 5.4 and 4.7cm/yr (Pt-A) and 9.4, 8.0 and 5.9cm/yr (Pt-B). Puberty onset was at 12.8(Pt-A) and 11.9(Pt-B) yrs. Height gain during puberty was 10.6(Pt-A) and 5.9(Pt-B) cm. Final height after 8.5 yrs of GH treatment was 130.5cm (-6.57SDS, Pt-A) and 134 cm (-4.58SDS, Pt-B).

Conclusions: To the best of our knowledge, this is the first report of final height in patients with AMDM after long-term GH treatment. Our patients with AMDM had GH/IGF1 profiles consistent with a degree of intrinsic GH resistance. GH treatment with doses 3-4 fold higher than conventional GH replacement increased their serum IGF1 levels to upper limit of age- and sex-related reference range, which was associated with increase to greatest height SDS (Pt-A -4.33SDS; Pt-B -2.76SDS) close to onset of puberty. Although this early improvement in height SDS enhanced their quality of lives, this was not sustained through puberty and probably failed to translate into improved final height.

P1-215

Acromesomelic dysplasia, type Maroteaux (AMDM): Impact of Long-term (8 years) High-dose Growth Hormone treatment on growth velocity and final height in two siblings

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Introduction: Acromesomelic dysplasia, type Maroteaux (AMDM) is a rare autosomal recessive skeletal dysplasia, characterized by severe dwarfism and disproportionate shortening of the extremities, predominantly affecting middle and distal limb segments. It results from loss-of-function mutations affecting the C-type natriuretic peptide (CNP) receptor (NPR-B), a transmembrane guanylyl cyclase receptor encoded by the *NPR2* gene. Resistance to growth hormone (GH) action has been suggested in AMDM. We previously reported an improvement in height velocity over 2 years of high-dose GH in two siblings with AMDM. We now present their final height outcomes.

Patients and Methods: Two siblings (Pt-A and Pt-B; consanguineous parents) presented in early childhood with severe disproportionate short stature and radiological signs of AMDM. Mother's height -0.65SDS; Father's height -2.08SDS. Subsequent genetic testing identified a novel homozygous *NPR2* variant (c.2548_2551delGAGA; p.[Glu850fs]) in both siblings. GH provocation testing (Glucagon) showed relatively high GH levels throughout (Pt-A 7.6 years, male, height -5.6SDS, peak/nadir GH-21.6/4.8mcg/L; Pt-B 5.7 years, female, height -4.5SDS, peak/nadir GH-12/1.3mcg/L). Serum IGF1 levels (60 and 37mcg/L)

P1-216

Birth anthropometry with cord blood insulin-like growth factor 1 and leptin in Korean appropriate-for-gestational-age infants born at ≥ 28 weeks' gestation

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Background: We investigated the relationship of birth anthropometry with cord blood insulin-like growth factor 1 (IGF-1) and leptin levels in Korean infants born at ≥ 28 weeks' gestation.

Methods: One hundred five appropriate-for-gestational-age (AGA) infants, defined as infants with birth weights (BWs) between the 10th and 90th percentiles for gestational age, were enrolled. Enrolled infants were stratified into three groups according to gestational age (GA) as follows: 28 to <34 weeks' gestation; 34 to <37 weeks' gestation; and 37 to <41 weeks' gestation.

Results: Between three GA-specific groups, there was significant differences in BW, birth length (BL), head circumference (HC), ponderal index, and cord blood IGF-1 and leptin concentrations ($p < 0.05$), but not in maternal pre-pregnancy body mass index (BMI), maternal pregnancy BMI, maternal age, and pregnancy-induced hypertension. GA and cord blood IGF-1 and leptin concentrations positively correlated with BW, BL, HC, and ponderal index in the univariate analysis. In the multivariate analysis, cord blood IGF-1 concentrations were independently associated with BW and BL. However, cord blood leptin concentrations were independently associated with BW, but not with BL, HC, and ponderal index.

Conclusions: In this study, fetal weight in the third trimester was independently associated with cord blood IGF-1 and leptin levels, but fetal height was only associated with cord blood IGF-1 level.

P1-217**Association between Nonalcoholic Fatty Liver Disease and Growth Hormone Deficiency in Patients with Childhood-onset Hypopituitarism**

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Background & Aims: Although, there has been reports demonstrating association between adult-onset hypopituitarism and development of nonalcoholic fatty liver disease (NAFLD), studies are lacking regarding the development of NAFLD in children and young adult with childhood-onset hypopituitarism. We aimed to identify association between NAFLD and hypopituitarism in these patients.

Methods: 76 Korean children and young adults with childhood-onset hypopituitarism and age-, BMI-matched 58 controls were recruited. Using FibroScan and/or magnetic resonance for fat quantification, we examined the stage of liver steatosis and liver fibrosis.

Results: Compared with controls, the prevalence of NALFD was significantly higher in patients with hypopituitarism. Six patients showed liver cirrhosis on FibroScan. Hypopituitary patients with NAFLD had were more obese and had longer duration without growth hormone (GH) replacement and had lower insulin-like growth factor I (IGF-I) and IGF-I/insulin-like growth factor binding protein 3 (IGFBP3) molar ratio compared to patients without NAFLD. Hypopituitary patients with liver fibrosis had longer duration without GH replacement compared to patient without liver fibrosis. After adjusting for BMI-SDS, odds ratios of duration without GH replacement, IGF-I SDS, and molar ratio of IGF-I/IGFBP3 for NAFLD were 1.764 (95% CI: 1.252, 2.485), 0.519 (95% CI: 0.315-0.856) and 0.001(95% CI: 0.000, 0.078), respectively. After BMI-SDS adjustment . Odds ratio of duration without GH replacement for liver fibrosis was 1.143 (95% CI: 1.003, 1.303)

Conclusions: The prevalence of NAFLD was significantly higher in patients with hypopituitarism. NAFLD including NASH and liver cirrhosis could be seen from childhood. Growth hormone replacement therapy demonstrated a possibility to prevent the development and progression of NAFLD in these patients.

P1-218**Lessons from a patient carrying both an 11p paternal duplication and 15q deletion, illustrating the roles of IGF2 and IGF1R in growth regulation**

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IGF2, a major actor which stimulates feta growth, is located within the imprinted 11p15 region, and 11p paternal duplications are usually associated with Beckwith Wiedemann syndrome, a rare condition usually associated with overgrowth. The IGF type 1 receptor binds both IGF-I and IGF-II to promotes cell proliferation and growth, and the *IGF1R* gene is located at chromosome 15q. Patients with deletions or mutations of *IGF1R* usually present with intrauterine and postnatal growth retardation.

We report an original association of complex genetic defects in a patient carrying both an 11p paternal duplication, and a 15q terminal deletion, including the *IGF1R*. Conversely to patients with *IGF1R* defects, the patient presented with normal birth parameters. However she presented with short stature after birth, microcephaly, intellectual disability and elevated IGF1 serum concentrations as usually described in patients with *IGF1R* anomalies.

This rare case allows a better comprehension of the IGF system in the pathophysiology of growth. We hypothesize that overexpression of IGF-II due to the 11p15 duplication, and the *IGF1R* defect may have compensated each other during fetal life. As postnatal growth was altered, this supports the hypothesis that the role of IGF-II is less important in post-natal growth, leaving IGF-I and growth hormone as the main actors after birth.

P1-219**The Therapeutic Effect of A Traditional Chinese Medicine Mixture in Rat Models with Precocious Puberty through Lin28/Let7 Pathway**

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Background: The onset of puberty is a complex biological process involving numerous factors under the control of the neuroendocrine pathways that are regulated as part of the hypothalamus-pituitary-gonadal (HPG) axis. The key step in puberty onset is activation of gonadotropin releasing hormone (GnRH) pulses and secretion. Recent evidence suggests that the Lin28/let7 pathway might be a critical regulator of GnRH release and that it might play an important role in regulating the onset of puberty.

Objective: The present study aims to investigate the effects of the nourishing “Yin” and purging “Fire” Traditional Chinese Medicine (TCM)herb mixture on precocious puberty and TCM may act through hypothalamic Lin28/let7 pathway expression in the precocious puberty model rats. Meanwhile, to confirm the relationship between Lin28/let7 pathway and puberty by overexpression Lin28a.

Design and Methods: Female rats were randomly allocated into untreated controls, the precocious puberty (PP) model group, the PP control group, and the PP + TCM group. Rats on postnatal day 5 were injected danazol to establish the PP model. From days 15 to 35, the rats in the TCM group were given the TCM twice daily. Vaginal opening, sex-related hormones, and body and reproductive organ weights were measured, and the expressions of hypothalamic *Lin28a* and *Lin28b* mRNA and *let7a* and *let7b* miRNA were detected.

Results: We found that at the onset of puberty, a decrease in ovary weight, an increase in the serum levels of luteinizing hormone and progesterone, and increased expression levels of hypothalamic *Lin28b* mRNA were observed in the PP + TCM group compared to the PP model group. The vaginal opening time was significantly delayed upon overexpression of *Lin28a*.

Conclusion: The mechanism by which the TCM treats precocious puberty is thus likely to be associated with inhibition of the hypothalamic Lin28/let7 signaling pathway and our findings provide in-depth insight into the relationship between the overexpression of *Lin28a* gene in the hypothalamus and the onset of puberty.

P1-220

Real-world data from electronic monitoring of adherence to growth hormone treatment in children with growth disorders: a descriptive analysis

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Poor adherence to long-term growth hormone (GH) treatment can lead to suboptimal clinical outcomes. The easypod™ connect eHealth platform enables healthcare professionals to obtain an accurate picture of real-world adherence by allowing patients to transmit adherence data to a database. Our aims were to assess adherence to r-hGH (Saizen, Merck KGaA, Darmstadt, Germany) treatment with the easypod connect platform in children from treatment start to 48 months and to investigate the effect of age and sex on adherence and the association between transmission frequency and adherence.

Patients transmitting >10 injections between January 2007 and February 2019 were analyzed. Adherence, calculated as mg injected/mg prescribed (dosage and settings defined by the care team) and categorized as high (>85%), intermediate (>56%–84%) or low (<56%), was assessed at months 1, 3, 6, 12, 24, 36 and 48 and then explored by puberty status (cut-offs at 10 years for girls and 12 years for boys) and sex. We calculated the transmission ratio (total

number of transmissions versus the total number of recorded days of easypod connect use) as a measure of patient engagement in disease management.

Longitudinal records were available for 13,553 patients. Overall, more patients had high adherence (n=9,578 [71%]) than medium (n=2,989 [22%]) or low (n=986 [7%]). Although the proportion of patients in the high adherence category decreased over time (from 87% at month 1 to 65% at month 48), at each time point more patients were in the high adherence category than in the medium/low adherence categories. Overall, a slightly higher proportion of girls had high adherence compared with boys (72% vs 69%); this trend was seen at each time point. Overall, the proportion of children with high adherence was greater in pre-pubertal children than in pubertal children (girls: 80% vs 70%; boys: 79% vs 65%) and a higher proportion of pubertal girls had high adherence versus pubertal boys (70% vs 65%). Children with high adherence had the highest transmission rates per number of days with information available: 0.029 versus 0.018 (medium) and 0.019 (low).

We used a validated method to fill an unmet need in recognizing the factors that affect adherence to r-hGH. We showed that high adherence to treatment over time and engagement with the device was seen in patients using easypod connect; however, some patient groups are at particular risk of lower adherence and engagement.

P1-221

Individual patterns of objectively measured adherence to growth hormone treatment and its effect on growth in prepubertal children with growth hormone deficiency

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The easypod™ electromechanical injection in combination with the easypod Connect platform electronically records and transmits, in real time, accurate, objective records of the date, time and dose injected for patients receiving Growth Hormone (GH) for growth disorders, limiting the risk of misreporting and allowing physicians to accurately monitor patient behavior.

The aim was to study individual patterns of adherence from start treatment up to 24 months and their effect on growth in prepubertal children with growth hormone deficiency (GHD). Data on adherence (=100% x number of injections taken/number of injections prescribed) and growth uploaded to the easypod Connect platform or collected by the Easypod Connect Observational Study (ECOS), a 5-year, Phase IV open-label study, were included. Inclusion criteria for adherence and growth were age before onset of puberty (<10 yrs in girls and <12 in boys). Additional inclusion criteria for growth were GHD and naïve to r-hGH treatment (ECOS study). Latent class mixed models with adherence as outcome and time after start of treatment (linear, centered quadratic) were constructed. This statistical method groups the patients into classes

based on their individual adherence pattern over time. Descriptive statistics for the adherence classes were provided in categories (low ≤56%, medium >56 – <85%, high ≥85%). Linear regression analyses were performed to compare change of height standard deviation score (HSDS) between adherence classes from start of treatment up to 6 to 24 months.

Adherence data were available for 6588, 3951, 2888, and 2068 patients and height data for 251, 223, 179, and 147 patients (GHD and naïve for GH treatment) between 0-6 months, 6-12 months, 12-18 months, and 18-24 months, respectively. The latent class mixed models constructed three classes. Class 1 (n=342) had on average a medium adherence between 0-6 months, a low adherence between 6-18 months and a medium adherence between 18-24 months. Class 2 (n=5968) maintained a high adherence. Class 3 (n=278) had on average a low adherence between 0-6 months, and adherence consistently increased until 18-24 months till a medium adherence. Significant differences in change in HSDS between 0-18 months (change HSDS= -0.52, p=0.002) and 0-24 months (change HSDS= -0.45, p=0.03) were found in class 1 compared to class 2. No other significant differences were found.

Three classes of individual patterns of adherence to growth hormone treatment over time were constructed. There was a significant effect of adherence on growth in prepubertal children with GHD.

Despite extensive investigation for the chronic constipation that started early in infancy, no cause was found. Subsequently it improved spontaneously. Teeth first erupted at the age of 2 years.

The routine screening for retinopathy of prematurity was negative. However, abnormal vascularization was noted at zone III in both fundi. On follow up, he was found to have small eyes with High hypermetropia and Flat cornea. Fundus exam and ERG confirmed the finding of retenitis pigmentosa and retina remained not completely vascularized with presence of retinal vessels in zone III.

He was referred to us for short stature at the age of 2 years where he was found to have high IGF1 and normal stimulated growth hormone peak. His short stature believed to be related to a syndromic cause at that stage. Other investigations showed normal brain auditory evoked potential and negative array CGH.

At age of 6-years, whole exome sequencing identified a novel homozygous mutation in IGF1R; NM_000875.4:c.431A>G (p.(Glu144Gly); which correlates very well with his phenotype. Segregation analysis done for both parents and healthy sibling showed all three are heterozygous of the same mutation.

At age of 6.5-years the child was started on growth hormone with a starting dose of (0.047mg/kg/dose six days in a week). His linear growth improved from -3 SD to -2.3 SD 3 years after treatment.

Conclusion: The reported case represent the complicated role that IGF1 play in the human linear growth, brain and eye development.

P1-222

A patient with a novel homozygous mutation in IGF1-R gene and response to growth hormone therapy

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Background: There are multiple factors affecting fetal growth, including maternal, fetal, placental and other environmental factors. Insulin like growth factor-1 (IGF-1) has a major role in promoting fetal and post-natal growth. It is also proven that IGF1 promote brain, inner ear and retinal development.

Case: We report a 9-years old boy born at 31 weeks of gestation to a consanguineous parents by cesarean section for severe oligohydramnios and severe IUGR. At birth weight 1120g (-3.57SDS), length: 36cm (-4.64SDS) and Head Circumference: 26cm (-2.57SDS). He had dysmorphic features; cowlick thick hair, touch of synophrys small face, up-slating Palpebral fissure, infraorbital crease, hypertelorism, thin upper lip and dimple chin. Hands and feet: clinodactyly; little finger two phalanges only, single palmar crease and partial overriding toes on the left foot.

He was followed from early in life for failure to thrive, visual impairment and chronic constipation. Diagnosed with global developmental delay and recently with ADHD. IQ assessment at age of 5.5 years was 86.

Growth and Syndromes (to Include Turner Syndrome)

P1-223

Tall stature and macrodactyly of the great toes due to a novel mutation in the natriuretic peptide receptor-2 gene

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Background: Mutations in the gene encoding the natriuretic peptide receptor-2 gene (*NPR2*) are responsible for monogenic growth disorders. Loss-of-function variants cause extreme short stature and skeletal dysplasia. Gain-of-function mutations cause tall stature with - in some cases - macrodactyly of the great toes, a Marfanoid habitus, arachnodactyly and scoliosis. We describe a novel gain-of-function mutation in exon 8 of *NPR2* in a family with tall stature and macrodactyly of the great toes.

Methods: History, clinical characteristics and investigations were collected from 3 patients, a mother and her two daughters. Fibroblasts from the mother, the previously described activating *NPR2* mutation patient with tall stature and a healthy volunteer with normal stature were obtained.

Results: Mother's height is 188.1 cm (+2.77 SD). She underwent epiphysiodesis to her great toes twice. At age 14 years she started treatment for 2 years with supraphysiological doses of estrogens in an attempt to reduce adult height. Menarche was at age 15. She has long thumbs with a positive thumb sign, minor ankle valgus, no scoliosis and no joint hypermobility. The eldest daughter is 6 years old. Her height is 132.6 cm (+1.96 SD), weight for height is -1.81 SD and sitting height to height ratio is -0.50 SD. She is known with pes planovalgus. She underwent epiphysiodesis of both great toes when she was 5 years old. The youngest daughter is 4 years old. Her height is 110.2 cm (+1.30 SD), weight for height is -1.42 SD and sitting height to height ratio is -0.66 SD. She has a history of minor gross motor developmental and speech delay. Both girls have markedly long great toes, ankle valgus and long thumbs with a positive thumb sign. Skeletal surveys showed pseudoepiphyses of the mid- and proximal phalanges of all fingers and both great toes, and mesomelia. Bone age was according to calendar age in both girls. The father of the girls is 178 cm, which results in a target height of 175 cm (+0.68 SD). Sequence analysis identified a novel heterozygous variant c.1444_1449del (p.Met482_Leu483del) in the *NPR2* gene of mother and her both daughters.

Conclusion: This case serie adds to the phenotypic spectrum of growth disorders associated with *NPR2* mutations, in particular gain-of-function variants. Functional tests of this variant to analyse the *in vitro* effect on cGMP and protein function are currently performed.

P1-224

The efficacy and adverse reactions of the letrozole or Gonadotropin releasing hormone analog combined with recombinant human growth hormone in short pubertal boys

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Objective: To explore the therapeutic effects and adverse reactions of a combination of letrozole or Gonadotropin releasing hormone analog (GnRHa) and recombinant human growth hormone (rhGH), compared with rhGH alone, in pubertal short boys.

Methods: Sixty-four pubertal short boys were divided into three groups, one group were treated with rhGH (rhGH group, n=21), one group were treated with the combination of GnRHa and rhGH (GnRHa group, n=19) and another group were treated with the combination of letrozole and rhGH (letrozole group, n=24). All boys had completed one or two years of treatments. The advancement of grow velocity, bone age (BA), height standard deviation score by bone age (Ht SDS_{BA}), while the body mass index (BMI), glucose and lipid metabolism, adverse reactions were measured.

Results: The ages of three groups were (12.79±0.98), (12.14±1.01) and (12.81±0.93) years ($P>0.05$), BA were (11.66±1.14), (12.97±0.90) and (13.27±0.75) years ($P<0.05$). The growth velocities of the first year were (10.75±1.56), (8.01±1.69), (10.11±2.19) cm/year ($P<0.05$), there were (9.44±1.53), (6.06±1.53) and (7.39±2.08) cm/year in the second year ($P<0.05$). The

increasing of BA of the first year were (1.67±1.01), (0.71±0.36) and (0.58±0.30) year/year ($P<0.05$), there were (1.13±0.43), (0.61±0.37) and (0.47±0.22) year/year ($P<0.05$), there were no significant difference in BA after treatment for two years. Increase of Ht SDS_{BA} in the first year were (0.05±0.88), (0.50±0.28) and (0.94±0.47), ($P<0.05$), there were (0.35±0.37), (0.26±0.29) and (0.81±0.46) ($P<0.05$) in the second year. There were no statistically significant difference of BMI, glucose and lipid metabolism between the three groups. During the treatment of combination group 3 boys suffered fractures, ultrasound bone density scan showed serious shortage of bone mineral density, after supplemental calcium and calcitriol, bone density increased within 3 to 6 months, no recurrence of fracture. There were no other adverse reactions in three groups.

Conclusion: Combination of letrozole and rhGH in pubertal short boys could inhibit BA progression, reduce growth slowdown, ameliorate Ht SDS_{BA} compare to the combination of GnRHa and rhGH, but bone density may be affected, and long-term follow-up is needed.

P1-225

The Phenotypic Spectrum of Kabuki Syndrome in Patients of Chinese Descent

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Background: Kabuki syndrome (KS) is a rare dominant disorder of transcriptional regulation with a complex phenotype including cranio-facial dysmorphism, intellectual disability, developmental delay, hypotonia, failure to thrive, short stature and variable cardiac and renal anomalies. Mutations in either *KMT2D* or *KDM6A* cause KS. While the phenotype of KS has been reported in many ethnicities, little is known about the phenotypic spectrum of KS in China.

Methods: Fourteen Chinese patients with genetically confirmed KS from 2 different hospitals were evaluated in detail in addition to eleven Chinese patients who were identified from the medical literature. The phenotype of these 25 Chinese patients was compared to that of 449 patients with KS from other ethnicities, published in the medical literature. In addition we explored the utility of Face2Gene, a commercially available facial recognition software in recognizing KS as the underlying diagnosis based on facial gestalt.

Results: All 25 patients with KS carried de novo, heterozygous likely pathogenic or pathogenic variants in either *KMT2D* or *KDM6A*. Three out fourteen patients were female, the mean age of genetic diagnosis was 4 years 1 month (3m-10.7y). Aspects of the facial gestalt including arched and broad eyebrows (25/25 100%), lateral eyebrows sparse or notched at one third of the distal end (18/18 100%), short columella with a concave nasal tip (24/25 96%) and large, prominent ears (24/24 100%) were more frequent in Chinese compared to non-Chinese patients ($P<0.01$). In contrast, the reported frequencies of microcephaly (2/25 8%), cleft lip/

palate (2/25 8%) and cardiac defects (10/25 40%) were lower in Chinese compared to non-Chinese patients. All patients in our cohort were recognized by F2G as KS.

Conclusion: The phenotypic spectrum in Chinese patients with KS may be different, although larger population studies in China are needed to confirm these preliminary findings.

P1-226

Response to growth hormone in very young children

([°] International Outcome Study and ANSWER

Program

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Objectives: Limited information is available on how very young children with growth hormone deficiency (GHD) respond to growth hormone (GH) replacement. We compared response to 1 year of GH therapy in children aged <2 years and prepubertal children aged ≥2 years.

Methods: The two non-interventional, multicentre studies, NordiNet[°] International Outcome Study (IOS) (NCT00960128) and the ANSWER Program (NCT01009905), evaluated the effectiveness of Norditropin[°] (somatropin; Novo Nordisk A/S) as prescribed in a real-world clinical setting. Height standard deviation scores (SDS) and target height SDS were based on national standards (NordiNet[°] IOS) or the Centers for Disease Control standard.

Results: Baseline characteristics [% or mean (SD)] for patients <2 years (n=506) vs. ≥2 years (n=9810): male: 59.7% vs. 69.3%; age at treatment start (years): 1.11 (0.57) vs. 9.09 (3.40); bone age/chronological age: 0.86 (0.99) vs. 0.81 (0.18); height SDS: -2.55 (1.77) vs. -2.39 (1.01); target height SDS: -0.20 (0.98) vs. -0.57 (1.02); GH peak (ng/mL): 4.07 (4.78) vs. 5.45 (4.68); IGF-I SDS: -1.34 (1.07) vs. -1.71 (1.59); birth weight (g): 3033.3 (680.7) vs. 3032.3 (697.1); birth length (cm): 48.3 (3.8) vs. 48.9 (3.9); GH dose (mg/kg/day): 0.035 (0.014) vs. 0.037 (0.011). Isolated GHD was less common in patients aged <2 years (54.6%) vs. ≥2 years (91.4%). Numbers of additional pituitary deficiencies were as follows (<2 years vs. ≥2 years): one: 24.11% vs. 5.92%; two: 12.85% vs. 1.34%; ≥3: 8.50% vs. 1.32%. After 1 year's treatment, all growth-related measurements improved in both groups: [mean (SD)] values: height SDS: -1.17 (1.50) vs. -1.73 (1.00); IGF-I SDS: 0.76 (1.42) vs. 0.41 (1.61); height SDS change from baseline: 1.44 (1.22) vs. 0.67 (0.49). After 1 year mean GH dose (mg/kg/day) was 0.035

(0.011) vs. 0.038 (0.012); median dose [P10; P90] was 0.034 [0.023; 0.049] vs. 0.036 [0.026; 0.053]. Adverse reactions (considered possibly related to treatment) were reported in 1.78% vs. 1.83%, and serious adverse reactions in 0.79% vs. 0.45% (<2 years vs. ≥2 years, respectively).

Conclusion: Children aged <2 years who required GH replacement had more severe GHD, as indicated by lower mean GH peak levels in stimulation tests versus prepubertal children aged ≥2 years. The prevalence of multiple pituitary deficiency was higher in younger children; therefore, clinicians must test them for additional pituitary deficiencies. Severe GHDs should be fully investigated and treated early, which is demonstrated by greater height gain after 1 year's treatment.

P1-227

Latest results from PATRO Children, a multi-centre, observational study of the long-term safety and effectiveness of Omnitrope[°] in children requiring growth hormone treatment

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Objectives: PATRO Children is an observational, international, longitudinal study of the long-term safety of a recombinant human growth hormone (rhGH; Omnitrope[°], Sandoz). In particular, the study will assess the impact of rhGH on glucose metabolism and risk of malignancies. Long-term effectiveness is a secondary objective.

Methods: The study population includes infants, children and adolescents receiving Omnitrope[°] therapy according to country-specific prescribing information. All adverse events (AEs) are monitored and recorded for evaluation of rhGH safety. Laboratory values (including glucose metabolism and anti-hGH antibodies) are requested at least once a year. Height standard deviation score (HSDS), height velocity (HV) and HVSDS are calculated according to country-specific reference tables.

Results: Over 13 years up to January 2019, data were included from 6710 patients at 301 sites in 14 countries. The mean (SD) Omnitrope treatment duration was 39.3 (27.0) months (approx. 3.3 years), with 1844 (27.5%) patients completing 5 years of treatment. Overall, 85.1% of patients were rhGH naïve and 14.5% had previously received rhGH treatment (0.4% data missing). Since the study start in September 2006, 3336 (49.7%) patients have reported 13588 AEs, with 674 AEs in 480 (7.2%) patients suspected to be treatment-related. Overall, 1553 AEs in 807 (12.0%) patients

were regarded as serious; of these, 81 events in 53 (0.8%) patients were suspected to be treatment-related. Drug-related serious AEs included type 1 diabetes mellitus (n=1 SGA patient, treatment discontinued), impaired glucose tolerance (n=2 SGA patients, treatment discontinued; n=1 GHD patient, dose reduction), malignant germ cell cancer (n=1 GHD patient, treatment discontinued), craniopharyngioma (n=1 GHD patient, no treatment interruption), and progression of a pre-existing neoplasm (n=1 GHD patient, n=1 patient with other indication; treatment interrupted in both). A positive anti-hGH antibody titer was reported post-baseline in one treatment-naïve patient (1.3% of patients tested post-baseline). Effectiveness data: following 4 years of treatment, the delta HSDS was +1.55 and +1.57 in prepubertal treatment-naïve GHD and SGA patients, respectively. At 4 years, delta peak-centered HVSDS was +4.42 and +3.68 in prepubertal treatment-naïve GHD and SGA patients, respectively.

Conclusion: The latest results from the ongoing PATRO Children study suggest that Omnitrope® is well tolerated and effective across pediatric indications; these findings will be reviewed by further analyses in the future.

P1-228

Broadening of the phenotypic spectrum of Coats plus syndrome: a patient presenting with extreme short stature as a hallmark feature

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Background and Aims: Coats plus syndrome (MIM # 612199) is a highly pleiotropic disorder particularly affecting brain, eye, bone and gastrointestinal tract. We describe the phenotype of a patient with severe growth failure where whole exome sequencing (WES) revealed compound heterozygosity for two mutations in the CTC1 gene.

Patient and Methods: The patient, the fourth child of healthy non-consanguineous parents, was born SGA (length -5.0 SDS, weight -2.7 SDS) with thumb malformations and bilateral narrowing of external auditory canals. Two siblings are healthy; one malformed sib died in utero. Postnatal growth was poor, IQ 65 and she had suffered five fractures. At 23 yrs she presented with a height of 117.7 cm (-7.0 SDS), progeroid appearance, elevated upper/lower segment ratio (1.2), BMI -2.3 SDS, head circumference -2.0 SDS, breast stage 2, thin skin and hair, microdontia/oligodontia, high palate, right thumb agenesis, left thumb hypoplasia and arthrogryposis. Further investigations showed hypergonadotropic hypogonadism (FSH 118, LH 49 IU/L, estradiol <1 pg/mL); IGF-I 193 ng/mL (ref 18-172); normal GH peak (22.5 ng/mL); bilateral radiohumeral luxofractures; agenesis of right thumb-metacarpal-scapoid; hypoplasia of left thumb-metacarpal; bicuspid aortic

valve; borderline bone mineral density (T-score -1.8 SDS); anemia (11.2 g/dL); uterine size of 34x10x13 cm (no endometrial lining); left ovary 17x9x13 mm (right ovary not visualized); large bilateral calcifications in basal ganglia on brain CT scan. Ophthalmological investigation was normal. Sequencing data of WES of patient and parents were analysed with a stringent post-sequencing annotation pipeline including *de novo*, X-linked recessive and recessive modes of inheritance filters.

Results: The recessive inheritance filter revealed a paternally (c.1617+5G>T) and maternally (c.724_727del,p.(Lys242Leufs*41)) inherited pathogenic variant in the CTC1 gene. Mutations in this gene are known to cause Cerebroretinal Microangiopathy with Calcifications and Cysts 1 (CRMCC1; Coats plus syndrome). The c.724_727del p.(Lys242Leufs*41) variant has been described in various patients; the c.1617+5G>T variant has not been reported. Splice predict software predicts the loss of the splice donor site which probably results in an in frame skip of exon 10.

Conclusion: Multiple characteristics (progeroid appearance, cerebral calcifications of the basal ganglia, osteopenia, bone anomalies, fractures, growth failure, anemia) are consistent with of Coats plus syndrome, but this patient is the first to present with complete hypogonadism and thumb anomalies. Retinal and gastrointestinal features are absent, confirming the large phenotypic variability of the syndrome. This case also illustrates the importance of WES in the diagnosis of children with extreme short stature.

P1-229

Endocrine evaluation of 29 Cornelia de Lange Syndrome patients (CdLS) patients

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Background: Cornelia de Lange (CdLS) syndrome (OMIM #122470) is a complex disease, characterized by distinctive facial features, failure to thrive, microcephaly, intrauterine growth retardation and anomalies in multiple organ systems. The complexity and severity of the endocrine commitment is variable. NIPBL, SMC1A, SMC3, RAD21 and HDAC8 genes, all involved in the cohesin pathway, have been identified to cause CdLS. There are few published studies on the endocrine evaluation in these patients; so our study is aimed at expanding our knowledge in this broad field of research.

Methods: A descriptive study of 29 Spanish patients diagnosed with CdLS was performed. We have analyzed the different metabolic, anthropometric variables. A complete study was carried out, genetic testing and analyzing different endocrine axes including thyroid, adrenal, growth, gonadal, lipid, phosphocalcic and metabolic study.

Findings: 65% of the sample are women and under eighteen years. 44.8% of patients have a history of intrauterine growth restriction (IUGR) in pregnancy, 50 % small for age gestational (SGA) at birth. The mean size of the sample is -3.33 ± 1.94 SD, far from the target size, with a difference of -2.82 ± 2.33 SD.

78 percent of the sample shows height measurements and 71% head circumference below -2 S.D.S. 3 patients have been treated with growth hormone with an increase in growth rate.

Approximately 50% of our patients harbor genetic variants in the NIPBL gene; however, in 30% of CdLS patients, no molecular alterations have been identified.

No thyroid and adrenal disorders have been observed. Twenty percent of the sample have decreased levels of growth factors, associated with younger patients and nutritional deficit. Impaired glucose tolerance (IGT) was found in 4 of the patients, 30% had increased LDL cholesterol levels. In turn, 27% of the sample shows insulin resistance. Regarding phosphocalcic metabolism, it is worth noting that 75% of patients show decreased levels of 25-OH-vitamin D and 60% of phosphores values below normal. 80% of the sample have decreased levels of testosterone. No other significant alterations have been found.

Interpretation: Our patients have growth retardation, most of them with prenatal onset, according to the clinical criteria of CdLS. Only few reports have commented on endocrine abnormalities in CdLS. In our sample of 29 CdLS patients serious alterations are not observed; however, it is important to carry out an endocrine evaluation, for each individual patient, in order to understand and be able to assess their metabolism adequately.

GH treatment was 9.1 ± 3.5 years (2.6-15.2). All girls had significant growth retardation (height SDS -2.87 ± 0.93) and a low growth velocity (4.7 ± 1.3 cm/year). Observed growth velocity in the first year of treatment was 7.8 ± 1.73 cm/year ($p < 0.001$). Height Δ SDS for 1 year of therapy was 0.49 ± 0.3 ($p < 0.001$). No significant differences in height Δ SDS and growth velocity after 1 year GH treatment were found between patients with either X monosomy or X-chromosomal abnormalities or mosaic variant 45,X/46,XX. GH therapy was stopped in 20 girls when growth velocity decreased to < 2 cm/year. Height Δ SDS was positively correlated with bone age retardation before treatment ($r = 0.5$, $p = 0.025$), first year height Δ SDS ($r = 0.499$, $p = 0.025$) and growth velocity ($r = 0.63$, $p = 0.003$). Correlation between height Δ SDS and mid-parental height ($r = -0.15$), mother height ($r = -0.09$), initial IGF-1 level ($r = -0.23$) was not revealed. No significant differences in reached height Δ SDS between girls with either spontaneous or induced puberty ($0.82 [0.62; 1.07]$ vs. $0.85 [0.74; 1.14]$).

Conclusions: For TS patients, GH treatment significantly increases growth rate. It was revealed that bone age before therapy, dynamics of growth velocity and growth SDS on the first year of treatment are the important predictive factors of therapeutic efficacy.

P1-230

Prognostic Factors of the Growth Hormone Therapy Effectiveness in Children with Turner Syndrome

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Objectives: To evaluate prognostic factors of the growth hormone (GH) treatment effectiveness in children with Turner syndrome (TS).

Methods: Retrospective observational study was conducted for 62 patients with TS (32 girls (52%) with 45,X karyotype, 8 (13%) with mosaic variant 45,X/46,XX, and 22 patients (35%) with structural abnormalities of X chromosome). All patients were treated with GH at a dose of 0.33 mg/kg per week continuously for a year or more. Anthropometrical and hormonal indicators of a growth axis (growth velocity (cm/year), height Δ SDS, bone age, insulin-like growth factor-1 (IGF-1) level) at GH therapy onset, after 1 year and at adult height achievement were estimated. The results were processed using SPSS.22.

Results: TS was diagnosed in patients with characteristic phenotypic signs according to the results of karyotyping at the age of 6.7 ± 5.07 (0.1-17.3) years. The chronological age at the start of

P1-231

Height and weight dynamics in preschool boys with constitutional delay of growth and puberty

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Background: Constitutional delay of growth and puberty (CDGP) is one of the most frequent norm variants in children presenting with short stature. Knowing the height, growth, and weight pattern of CDGP in the first years of life is important to distinguish CDGP from growth hormone deficiency (GHD) or other diseases.

Methods: We studied height and weight in the first 5 years of life in 54 boys with CDGP including measurements of adult height and weight at the age of ≥ 20 years.

Results: Height-SDS and BMI-SDS decreased between birth and chronological age of 2 years and increased between puberty and final observation. While at 1 year of age 7.7% of the boys were underweight, 26% of boys with CDGP were underweight at 2 years. In contrast, at adult age 77.8% of the boys had a BMI in the normal range and 16.7% were underweight.

Table: Height, height-SDS, weight, BMI, and BMI-SDS over time

Time point	Height [cm]	Height-SDS	Weight [kg]	BMI [kg/m^2]	BMI-SDS	p-value height-SDS compared to previous observation	p-value BMI-SDS compared to previous observation
birth	51 (49–53)	−0.36 (−1.03–−0.30)	3.18 (2.84–3.42)	12.0 (11.0–13.0)	−0.37 (−1.36–−0.33)	—	—
6 months	68 (65–69)	−0.70 (−1.18–−0.12)	7.67 (7.09–8.20)	17.0 (15.7–17.7)	0.07 (−0.84–−0.87)	0.004	n.s.
12 months	73 (71–75)	−1.16 (−15.4–−0.42)	8.93 (8.35–9.52)	16.6 (16.0–17.3)	−0.08 (−0.76–−0.53)	<0.001	n.s.
2 years	84 (82–87)	−1.39 (−2.02–−0.47)	11.1 (10.5–12.4)	15.5 (14.6–17.0)	−0.68 (−1.45–−0.50)	0.035	0.031
4 years	99.0 (96.1–102.0)	−1.32 (−1.89–−0.37)	14.4 (13.6–16.0)	14.9 (14.1–15.6)	−0.66 (−1.44–−0.02)	n.s.	n.s.
5 years	106.3 (103.0–110.0)	−1.11 (−1.89–−0.21)	16.4 (15.5–18.2)	14.5 (14.0–15.5)	−0.82 (−1.35–−0.06)	n.s.	n.s.
visit clinic [~14 years]	147.6 (142.8–154.5)	−2.24 (−2.68–−1.39)	36.0 (31.9–45.0)	16.8 (15.3–18.6)	−1.35 (−1.91–−0.48)	<0.001	<0.001
Last observation [~22 years]	174.6 (170.8–179.0)	−0.66 (−1.21–−0.01)	66.5 (60.0–73.7)	21.9 (19.9–23.9)	−0.14 (−0.92–−0.40)	<0.001	<0.001

Data as median and interquartile range, n.s.: not significant

Conclusion: Height and weight deflection in CDGP occurs already during the first two years of life. Leanness is a typical feature of CDGP during childhood, while boys with CDGP frequently have a healthy weight status as adults. This characteristic pattern of growth and weight changes might be helpful to distinguish CDGP from other diseases with short stature.

Method: The clinical and genetic characteristics of two Chinese children from unrelated families with acromelic dysplasia were analyzed retrospectively, including one case each of GD and AD. The microfibrillar structure and the level of TGF β in GD individual are also studied simultaneously.

Results: (1) Patient 1 was a 7-year and 1-month-old boy with GD. He presented severe short stature without intellectual disability, full cheeks, flat nose, thick lips, short neck, short limbs and both of his hands were stubby with claw deformity and limited extension of fingers. He had mild pulmonary stenosis and his bone age was 4-year old. A heterozygous missense mutation c.5284G>A (p.Gly1762Ser) of *FBN1* gene was detected by next-generation sequencing (NGS), which had been reported previously. The microfibrillar structure was no significant difference from controls, while the level of TGF β was significantly higher than controls. (2) Patient 2 was a 2-year and 6-month-old girl with AD. She presented severe short stature with normal intellectual function. She had a round face, narrow palpebral fissure, flat nose, thick lips, short neck, short limbs, small hands, small feet and thickened skin but without limitation of joint range of motion. Her fingers were short with claw deformity and palm hypertrophy, and her bone age was nearly 2-year old. A heterozygous missense mutation c.5159G>A (p.Cys1720Ser) of *FBN1* gene was detected by NGS, which had never been reported.

Conclusion: Both GD and AD can be caused by mutations of *FBN1* gene. The mutation c.5284G>A (p.Gly1762Ser) of *FBN1* gene presents pleiotropic nature, and enhanced TGF β signaling plays an important pathophysiologic role. A novel missense mutation c.5159G>A (p.Cys1720Ser) of *FBN1* gene is identified in our study. Further research is required to understand the mechanism of *FBN1*-related acromelic dysplasia.

P1-232**Two Chinese Children with FBN1-Related Acromelic Dysplasia**

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Background and Aims: Geleophysic dysplasia (GD) and acromicric dysplasia (AD) are rare skeletal dysplasia belonging to the group of acromelic dysplasia and are both characterized by severe short stature, short hands and feet, stiff joints, facial anomalies and some radiological manifestations, including delayed bone age, shortened long tubular bones and ovoid vertebral bodies. Patients with GD clinically present the characteristic “happy” facial features, cardiac valvular abnormality, progressive hepatomegaly and tracheal stenosis. The clinical features of AD are usually similar to GD but without cardiac valvular abnormality. This study reported two Chinese children with acromelic dysplasia due to *FBN1* gene mutations.

P1-233**Growth patterns over two years after birth according to the birth weight and length percentile in children born preterm**

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Purpose: This study aimed to analyze growth patterns during the first two years after birth according to the birth weight and length percentile in children born preterm, and to investigate factors affecting postnatal growth of these children.

Methods: Eighty-two preterm neonates with a gestational age below 37 weeks who followed up until 24 months of corrected age (CA) were retrospectively reviewed. Length, weight and head circumference were measured at birth, 6, 12, 18, and 24 months. Data were analyzed between children born small for gestational age (SGA) and those born appropriate for gestational age (AGA).

Results: Most preterm infants born SGA grew higher than -2 SDS in length during the first 6 months. Compared to AGA group, SGA group had a low length SDS at 24 months of CA (-0.87 ± 1.11 vs -0.09 ± 1.06 , $P=0.01$). There was no significant difference in the rate of growth failure (length standard deviation score [SDS] <-2 at 24 months of CA) between SGA and AGA group (15.8 % vs 4.3%, $P=0.13$). Multivariable logistic regression analysis showed that length below 10th percentile at birth (odds ratio [OR], 47.47; 95% CI, 2.02-1117.13, $P=0.02$) and longer duration of in neonatal intensive care (NICU) (OR, 1.06; 95% CI, 1.01-1.11, $P=0.02$) were associated with a decrease of length SDS (lower than -1) at 24 months of CA.

Conclusion: Whether SGA or not, most of preterm infants grow higher than -2 SDS during first 2 years: Birth length SDS and length velocity are one of the important factors affecting length SDS at 24 months of CA in children born SGA.

P1-234**Identification of syndromal macrosomia: Macrocephaly, but neither height nor weight data are useful in the detection of pediatric PTEN hamartoma Tumor Syndrome (PHTS)**

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Background: PTEN Hamartoma Tumor Syndrome (PHTS) encompasses different syndromic disorders which are associated with autosomal-dominant mutations of the tumor suppressor gene *PTEN*. Patients are at high risk to develop benign and malignant tumors. Macrocephaly is a diagnostic feature, but there is a paucity of data on prevalence, degree and development during growth. Charts for length, weight and head circumference for this rare disorder do not yet exist.

Methods: Patient data for length, weight and head circumferences (HC) were collected from repeated medical exams starting at birth. Growth charts were generated and compared to German reference data. Standard deviation scores (SDS) of head circumference and BMI were calculated.

Results: We included 23 patients (8 female, 15 male) with molecular proven *PTEN* mutation. Most male patients showed macrocephaly already at birth (11/15), whereas only one female patient had documented congenital macrocephaly. At the age of two years all patients exhibited a head circumference > 97th percentile. Stratified for different ages median HC-SDS of male patients were between +3.3 and +5.5 (mean 4.2 SDS) and for female patients between +2.7 and +4.1 (mean 3.2 SDS). Length, weight and BMI charts for both sexes were mostly within the normal range.

Conclusion: Macrocephaly, but not length, weight or BMI help to identify *PTEN* patients. The increase in HC in PHTS patients is developing early in life and is more pronounced in males than in females. This might explain why more male patients are detected during childhood.

P1-235**Development of a measure for the impacts of achondroplasia on children's daily functioning and well-being**

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Background: Research on the impacts of achondroplasia on children's functioning and well-being is limited. The purpose of the study was to investigate the impacts of achondroplasia on children's daily lives to support the development of an impact measure of achondroplasia on children's functioning and well-being.

Methods: Individual telephone interviews and one parent focus group were conducted in the United States (US) and Spain with parents of children with achondroplasia aged 2 to <12 years using a semi-structured interview guide. Interview and focus group transcripts were analyzed using an adapted grounded theory approach to identify important concepts and themes and to inform the development of a validation-ready impact measure.

Results: Thirty-six parents (n=31 mothers; n=5 fathers) of children aged 2 to <12 years with achondroplasia participated in interviews or the focus group (Spain, n=11; US, n=25), including seven parents with achondroplasia. Analyses identified daily functioning, emotional well-being, social well-being, and participation in school as important impact domain. The most frequently reported impacts on children's daily functioning included difficulty reaching objects or high places (89%, n=32), toileting (67%, n=24), bathing/washing or grooming (58%, n=21), running (56%, n=20), walking (50%, n=18), being physically active (47%, n=17), and dressing/undressing (47%, n=17). For the emotional well-being domain, the most frequent impacts were feeling different (53%, n=19), feeling frustrated (47%, n=17), feeling sad (39%, n=14), feeling embarrassed/self-conscious (33%, n=12), and feeling angry/mad (33%, n=12). In the social well-being domain, the most frequent impacts

included difficulty participating in sports or physical play (86%, n=31), being treated as younger than age (83%, n=30), negative attention in public (e.g., staring/pointing; 64%, n=23), experience of teasing/bullying (64%, n=23), participation in social activities (64%, n=23), keeping up with other children their age (58%, n=21), and being stigmatized (56%, n=20). Among school-aged children (aged 5 to <12 years; n=25), key impacts on school participation included missed time/days at school (76%, n=19), limited/modified participation in physical education class (68%, n=17), and issues participating in class/school work (40%, n=10).

Conclusion: The study provides evidence to support the content validity for an impact measure of achondroplasia on children's daily functioning and emotional and social well-being. Understanding and assessing the impacts of achondroplasia on children's general functioning and well-being, which may be improved with treatment, is critical in the clinical management of achondroplasia as new treatments are being developed.

Multisystem Endocrine Disorders

P1-236

Serum endocan levels as a marker of endothelial dysfunction in Turner syndrome and correlation with cardiac findings

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Background: The most common reason for the increased mortality and morbidity in TS, which results from partial or complete deficiency of an X chromosome in a female, is acquired cardiovascular disease, which is the result of endothelial dysfunction that causes atherosclerosis. Endocan, an inflammatory marker, has been found elevated in several diseases with endothelial dysfunction (ED). There is no study of endocan levels in TS.

Objective: To investigate the significance of serum endocan level in evaluating ED in TS.

Methods: 41 girls with TS and 25 healthy females were enrolled. Patients were examined, weight, height, waist circumference (WC) were measured, body mass index (BMI) values were calculated, systolic (SBP) and diastolic blood pressure (DBP) were measured and expressed as SDS. Samples for serum endocan levels (pg/mL) were obtained and the patients underwent ultrasound (USG) evaluation for measurement of carotid intima media thickness (cIMT) (expressed as SDS) and flow mediated dilation (FMD) (%). Karyogram, fasting blood glucose and insulin levels, total cholesterol (TC), high density lipoprotein (HDL), low density

lipoprotein (LDL), triglyceride (TG), C-reactive protein (CRP), thyroid hormone and antibody levels and echocardiogram findings were obtained from patient files. Homeostatic model assessment – insulin resistance index (HOMA-IR) was calculated.

Results: Mean age of the patients was 14.7 ± 3.6 years. Mean age of the controls was 11.1 ± 2.9 years ($p = 0.001$). SDS values were used instead of absolute values wherever possible to minimize the effects of age difference on our results. Height SDS of the study group was lower than the control group ($p=0.001$). WC SDS ($p=0.033$) and BMI SDS ($p=0.003$) of the study group were higher than that of the control group. The study group had a higher SBP SDS ($p=0.001$) and DBP SDS ($p=0.001$). The study group had higher levels of TC ($p=0.001$), LDL ($p=0.025$), fasting insulin ($p=0.027$) and HOMA-IR ($p=0.016$). Both groups had similar endocan levels, cIMT and FMD. Karyotype, pubertal status, cardiac anomalies, IR and thyroiditis did not alter endocan, cIMT or FMD. Overweight and obese patients were found to have lower FMD than non-overweight patients ($p=0.038$) and the controls ($p=0.018$). WC ($r=-0.348$, $p=0.005$) and BMI SDS ($r=-0.368$, $p=0.002$) were found negatively correlated with FMD.

Conclusion: Our data do not support the use of endocan levels to evaluate for ED in TS. Lower FMD in obese TS patients and negative correlation of FMD with BMI and visceral obesity show that controlling obesity is important for future vascular pathology.

P1-237

The Effects of Fetal Electromagnetic Field Exposure on Expression of Anxiety Behavior and Associated Genes in Adolescent Period

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The stimulants that the mother is exposed during pregnancy may affect the baby in the future. Electromagnetic field exposure is an important external stimulus that we are subject to. In addition to the interaction of the earth and the sun with the magnetic field of man; nowadays the intensive use of electrical appliances, computers, mobile phones and internet, how electromagnetic field exposure may affect future generations will only occur in the continuation of our generation. It is thought that electromagnetic fields have many effects and may affect anxiety behaviors. In our study, we investigated the effects of low frequency electromagnetic field exposure on the anxiety-related genes and protein levels and also on anxiety-like behaviors during adolescent periods of offspring. Our study groups consist of rats exposed to the pulsed electromagnetic field at a frequency of 50 Hz (usually the power frequency in the networks in Europe) for 2 hours a day at the first, second and third weeks of gestation, male and female groups born out of mothers exposed to the electromagnetic field during pregnancy and controls for every group that were not exposed to any treatment. Anxiety-like behaviors were evaluated by using an elevated

plus maze test after electromagnetic field treatments. After the behavioral test, hippocampus tissues of all groups were extracted. First, RNA and protein isolation were performed from hippocampus tissues. Gene expression profiles were evaluated with Real time PCR method protein expression levels were evaluated by western blot method.

In our study, anxiety-like behavior was observed in the elevated plus maze test in group of males born from rats which were exposed to pulsed electromagnetic field during pregnancy. Dopamine D1 receptor, fos, 5-HT1A, Grin1, Grin2a, Grin2d, Adora1 and Adora2a gene expressions suppressed and only nervous system development and plasticity associated BDNF gene expression induction were observed in gene expression analysis. This increase in expression in the BDNF gene also supports our western blot.

Results: Our data suggest that the exposure of electromagnetic field during pregnancy may make the offspring more sensitive to anxiety in the future, but it is foreseen that more detailed and advanced studies are needed in the light of the results obtained in terms of gene expression.

P1-238

Positive correlation between circulating irisin concentrations and homeostatic model assessment for insulin resistance (HOMA-IR) in women with Polycystic Ovary Syndrome: a Meta-analysis

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Background: Irisin has emerged as a potential mediator of energy expenditure that may improve adiposity and glucose homeostasis. Irisin's metabolic benefits in animal models are convincing, but only promising regarding humans. Irisin's secretion by and its potential roles in several tissues have been associated with insulin resistance (IR). In modern societies, health problems associated with IR are quite common. One such condition, the enigmatic polycystic ovary syndrome (PCOS) has attracted growing interest in irisin as a potential novel biomarker of the syndrome. Studies of circulating irisin in patients with PCOS have reported discrepant results.

Objective: A meta-analysis was performed to compare circulating irisin concentrations between PCOS and control women, and to explore the possible relation of irisin and IR, by associating this hormone with the homeostatic model assessment for IR (HOMA-IR).

Methods: Following the PRISMA guidelines, an extended search of the PubMed/Medline, Google Scholar and Web of Science databases was performed to identify all articles published in English language pertaining to circulating irisin in women with PCOS. In addition, the references of selected papers were searched manually. Search terms were "irisin" and "PCOS" or "irisin" and "polycystic ovary syndrome". Retrieved articles were eligible for

inclusion in this meta-analysis if they included (i) women with PCOS and control women, pooled from the general population and (ii) measurements of circulating (plasma or serum) irisin concentrations in women with and without PCOS. Articles were excluded if (i) published repeatedly or (ii) data were incomplete. Statistical analysis was conducted with the use of the Review Manager software (Version 5.2, the Nordic Cochrane Centre, Copenhagen, Denmark).

Results: Eleven studies, out of 16 extracted studies, were included in the meta-analysis and involved in total 1,686 women: 1,017 PCOS patients and 669 non-PCOS controls. A random effects model revealed a moderate estimate of effect size (SMD: 0.27, 95%CI: -0.13 to 0.67), indicating that circulating irisin concentrations did not differ significantly between PCOS women and controls. Another random effects model (four studies) revealed a moderate estimate of correlation and a statistically significant positive correlation between circulating irisin concentrations and HOMA-IR (Correlation: 0.372, 95%CI: 0.0843 to 0.603, $P=0.012$).

Conclusion: Irisin may play an important role in PCOS in relation to the inherent IR of the syndrome. This association requires further clarification in well-designed large-scale studies in women with PCOS, pending improvement of circulating irisin detection methodology.

P1-239

Unusual Presentation of Autoimmune Polyglandular Syndrome Type 1 (APS1)

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Introduction: Autoimmune polyendocrinopathy type 1 (APECED) is an autosomal recessive disease caused by loss of function mutations of autoimmune regulatory (AIRE) gene. Characteristically, early onset ectodermal dysplasia, mucocutaneous candidiasis is followed by hypoparathyroidism and primary adrenal insufficiency usually within the first two decades. Although clinical features may be variable, recently, it is suggested that population characteristics and natural course and clinical features of the disease are associated. Herein a case of APECED referred with growth retardation, arthritis, diarrhea and pneumonia, followed by type 1 diabetes and adrenal insufficiency is presented.

Case: The patient presented with chronic diarrhea when he was 9 years old. At the age of 10, he was referred with swelling, pain and limited movements of the left knee and was diagnosed with arthritis. At the age of 13.5, he was admitted for necrotizing pneumonia, had severe short stature. He was started on intravenous antibiotics and immunoglobulin. Family history revealed that the

patient was the third child of a consanguineous couple, and had two healthy siblings. His mother and aunt also had short stature. On physical examination he had severe short stature (117.6 cm, -7.66 SDS) and malnutrition (17.7 kg, -5.22 SDS); immature facial features, high-pitched voice, dry, hyperpigmented skin. Pubertal stage was Tanner 1. He had normochromic normocytic anemia, and lipid soluble vitamin deficiency, liver transaminases were elevated. Baseline immunologic examination and sweat chlorine levels were within the normal range. Bone age was 8 years, IGF-1 and IGFBP3 levels were very low (<-3SD).

Colonoscopic ileum biopsy revealed eosinophilic ileitis. During follow-up, hyperglycemia was detected, simultaneous serum insulin and c-peptide levels were low, HbA1c was normal, anti-GAD autoantibodies were elevated (72,37 U/L). A preliminary diagnosis of IPEX Syndrome was ruled out with *FOXP3* gene sequencing. The patient was examined for other autoimmune endocrinopathies however he did not have hypoparathyroidism or hypothyroidism. Primary adrenal insufficiency was suspected and peak cortisol of 14 mcg/dl during ACTH test established the diagnosis; hydrocortisone replacement was initiated. Next-generation sequencing(NGS) revealed an insertion leading to a frameshift mutation in the *AIRE* (autoimmune regulator) gene (c.208_209insCAGG-p.Asp70fs). Immunosuppressive therapy was started.

Conclusion: Chronic diarrhea causing resistant metabolic acidosis, malnutrition and type 1 diabetes in the first decade is uncommon in APECED's. This case is important as it emphasizes its phenotypic variability. The molecular alteration caused by frameshift mutation may explain the severity of the phenotypical features of the patient that would be expected in IPEX.

P1-240

Association of Tuberous sclerosis complex (TSC) and Insulinoma in a pediatric patient

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Introduction: Tuberous sclerosis complex (TSC) is an autosomal dominant condition caused by a loss-of-function mutation in tumor suppressor genes TSC1/TSC2 which are involved in the inhibition of mTOR signaling implicated in cell proliferation. Major clinical features includes cardiac rhabdomyomas, renal cysts, epilepsy associated to cerebral dysplasia evidenced by cortical tubers and skin manifestation as: angiofibromas, fibrous plaques and the Shagreen patch. Around six cases of insulinoma had been described in adult population with TSC. Childhood insulinoma is rare, occurring either in isolation or in association with multiple endocrine neoplasia type 1(MEN1), 5-10% are malignant. Diagnosis of insulinoma is based on the presence of Whipple's triad, detectable insulin during hypoglycemia and is located by MRI scan or 6-L18F-fluorodihydroxyphenylalanine(18-F-DOPA)PET-CT.

Objective: To present a 14-year-old girl with diagnosis of TSC and insulinoma

Case Report: A girl with diagnosis of TSC had a prenatal diagnosis of cardiac rhabdomyomas. She was born at term, with normal weight/length, postnatally ultrasound confirmed rhabdomyomas and detected unilateral multiple renal cysts. At one-year-old presented absence epilepsy, the cerebral MRI showed abnormalities consistent with cerebral tubers. Learning was normal. At 14-years-old started with episodes of confusion with slurred speech upon awakening after prolonged sleeps in weekend. Although the electroencephalograph was normal, changes in anti-epilepsy pharmacotherapy were made in an attempt to resolve these episodes without improvement during seven months until hypoglycemia was detected during one episode.

Upon physical examination normal stature and BMI, angiomyoma, fibrous plaque and Shagreen patch were found. A fasting tolerance test allowed to detect after 10 hours: Glucose 41mg/dl(55-110), insulin 28,7mUI/l (<1) C-peptide 4,6 ng/ml(0,8-5,2). Cortisol 109 nmol/l(101-536), GH 4,76ng/ml (>5), IGF1: 414ng/ml(220-996). PRL:7,7 ng/ml(0-14), Ca:9,3 mg%(8,4-10,2), P:2,5mg% (2,5-5,0), PTH:18,04 pg/ml (10-55). Hyperinsulinism was diagnosed without evidence of MEN1. Abdominal MRI scan showed a low-signal-density on T1-weighted-images and a high-signal-density on T2-weighted-images that enhanced with contrast of 27x23x20 mm in the pancreas body with concordant finding in the 18-F-DOPA-PET-CT scanning of a increased focal uptake(SUV max 23,3).

She underwent partial pancreatectomy with perioperative frozen section. Histology diagnosis of insulinoma surrounded by a fibrous capsule without infiltration confirmed diagnosis of benign insulinoma. Postoperatively euglycemia, elevated β -OHbutyrate:0,39(< 0,35mmol/l) and NEFA:0,64 mmol/l (0,09-0,60) after prolonged fasting suggested absence of recurrence during 6 months of follow-up.

Conclusion: Insulinoma in TSC should be consider in patients with changes in neurologic symptoms, normal EEG without response to pharmacotherapy.

P1-241

A novel DCAF17 homozygous mutation in a girl with Woodhouse-Sakati syndrome and its role in the endocrine glands

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Background: 46,XX gonadal dysgenesis is a rare condition linked to delayed puberty, absence of spontaneous pubertal development, and primary amenorrhea related to hypergonadotropic hypogonadism (Hh). External genitalia are typically female with no ambiguity. Although ovarian development is an active process with multiple gene involvement, the genetic etiology of this condition is usually unknown. *DCAF17* has recently been implicated

in the development of both male and female gonads, thus resulting in hypogonadism. This condition represents one component of Woodhouse-Sakati syndrome (WSS), arising from mutations in the *DCAF17* gene, an extremely unusual autosomal recessive disorder.

Methods: A 16-year-old girl with consanguineous parents presented due to delayed puberty, absence of spontaneous pubertal development, and primary amenorrhea. Hypogonadism was present, in the form of Hh. Whole-exome sequencing was used to identify the genetic etiology underlying the hypogonadism.

Results: A novel homozygous variant c.1091+1G>A was detected in *DCAF17*. Both parents were sequenced and identified as heterozygous for the same mutation.

Conclusions: Various manifestations of WSS do not emerge until later in life, making diagnosis in pediatric cases particularly difficult, as in the present report. *DCAF17* may also be implicated in the genetic etiology of 46,XX gonadal dysgenesis.

P1-242

Basal metabolic rate in polycystic ovary syndrome: a meta-analysis

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Background: While polycystic ovary syndrome (PCOS) is implicated with insulin resistance and obesity, little is known about the abnormal energy imbalance contribution to the disease. Basal metabolic rate (BMR) represents the energy expenditure by a normal subject at rest, remote from eating, in a thermally neutral environment, reflecting the 50–70% of total daily metabolism. The relevant literature is limited with conflicting results- worth meta-analysis approach.

Aim: To evaluate the basal metabolic rate in PCOS by meta-analysis.

Methods: Data collection in Pubmed has been performed in April 2019 with keywords “BMR in PCOS”. After PRISMA protocol, four cross-sectional studies on PCOS vs controls (BMI, age adjusted) were included in the analysis. Meta-analysis was performed with SPSS software and the summarized effect size of BMR is evaluated with Hedge's g correction for small samples.

Results: Studies on patients vs non-patients met the inclusion criteria. A non-significant fixed effect of $g=0.043$ 95% CI (0.264, -0.177) is calculated, whilst, if we exclude one study after bias and weighing control, the effect size becomes significant: $g= -0.31$ 95% CI (-0.069, -0.551).

Conclusions: BMR is decreased in the PCOS syndrome, thus, energy homeostasis and metabolism imbalance are implicated to the syndrome.

P1-243

A nation-wide questionnaire survey targeting Japanese pediatric endocrinologists regarding transitional care in pediatric and adolescent cancer patients

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Background: While existing guidelines recommend long-term follow-up of childhood cancer survivors (CCS), transitional care among pediatric and adult endocrinologists has not been established in Japan.

Objective and hypotheses: To know the present situation and to cultivate a better understanding, we had conducted a nation-wide survey targeting Japanese pediatric endocrinologists.

Method: We had conducted the questionnaire survey regarding transitional care in pediatric and adolescent cancer patients. The survey was sent to 183 Japanese Society for Pediatric Endocrinology (JSPE)-certified councilors (137 institutions) who were asked to self-evaluate their medical examinations and report problems in their follow-up. If multiple councilors belonged to the institution, one representative could present their voice. This work was supported by a Grant-in-Aid for Scientific Research (Japan Society for the Promotion of Science), and was in collaboration with the CCS committee of the JSPE and Research for Promotion of Cancer Control Program (Ministry of Health, Labour and Welfare).

Results: A total of 131 responses (male 102, female 29), representative of 174 councilors, were obtained. The response rate was 95% (174/183) per councilor. Ninety-two percent of respondent had experience in medical care for pediatric and adolescent cancer patients. Sixty-three percent had experiences in their transitional care. However, the number of patients referred to adult clinicians was minimum. Eighty-nine percent of respondents agreed the existence of adult endocrinologists who could accept follow-up of these patients in their region, but sixty-eight percent felt shortage. Pediatric endocrinologists highlighted difficulties in medical examinations dealing with infertility (84), obesity (47), pregnancy/delivery (40), gonadal dysfunction (40), and second cancer (35). The main burdens facing physicians were staff shortage, lack of clarity of their task, insufficiency of knowledge, patient-doctor relationship, and insufficient medical information. The main burdens to patients were supposedly multiple-field physical problems, financial and time burdens, infertility, unawareness of their health-related problems, and lack of recognition of the importance of long-term follow-up. Sixty-six percent wrote their comments, which include poor collaboration between endocrinologists and oncologists, shortage of information about cancer treatment, difficulty in approach method, lack of economical support, and regional differences. List of the main necessities was as follows: education program for physicians, collaboration between healthcare

providers, training coordinators, information sharing, financial support system, social support in education and employment.

Conclusion: In this nationwide questionnaire survey, Japanese pediatric endocrinologists mentioned the necessity for interdisciplinary communication amongst healthcare providers and socio-economical support to pediatric and adolescent cancer patients.

P1-244

Two Different Endocrine Cancer, One Disease; DICER-1 Mutation

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Autosomal dominant DICER1 mutations are among the causes of early-onset familial cancer. DICER1 mutation has been shown in pleuropulmonary blastomas as well as ovarian tumors, thyroid, parathyroid, pituitary, adrenocortical and testicular tumors. It is important to be aware of the risk for the development of other cancers in the follow-up of these cases.

Cases

Case-1: Previously known to be healthy 8,5-year-old girl presented with complaints of deepening voice and hirsutism. On physical examination, she was significantly above the familial target height percentile. Thelarche was consistent with Tanner stage 1, while pubic hair was stage 5. The size of the clitoris was markedly increased by 3x1cm. Increased muscle mass was remarkable. In Laboratory evaluation, total testosterone (231.6 ng/dl) was found significantly high. The ultrasonographic evaluation revealed a mass of 43 mm in the left adrenal area. The patient was operated and pathological evaluation was consistent with adrenocortical carcinoma. When the family history was detailed, it was learned that the parents were 1st-degree cousins and her aunt was treated for thyroid cancer. Genetic analysis revealed DICER1 mutation. During the follow-up visits, a simple ovarian cyst with the diameter of 3cm was detected. Lactate dehydrogenase, alpha-fetoprotein, beta-human chorionic gonadotropin levels were all normal. After 2 months the ovarian cyst disappeared spontaneously.

Case-2: A 6.5-year-old girl was admitted to the emergency service with abdominal pain. A mass was palpated in the abdomen and other system examinations were normal. Pubertal development was consistent with Tanner stage 1. Lactate dehydrogenase and CA-125 levels were elevated. Ultrasonographic imaging revealed a mass lesion of 15 cm in diameter with right adnexal origin. The patient had been operated. Pathological evaluation of the mass was consistent with Sertoli-Leydig cell tumor. During follow-up, a solid nodule (8 mm in long axis) in the left lobe of the thyroid gland was detected incidentally. Fine needle aspiration biopsy revealed a benign lesion but because of coexisting of these two clinical conditions genetic analysis was performed. A germline mutation was detected in the DICER1 gene. Follow-up of both patients continues.

Conclusion: As seen in our cases, DICER mutation should be considered in the presence of multiple organ involvement in endocrine cancers and other endocrine organ pathologies should be kept in mind during the follow-up period.

P1-245

PTEN Hamartoma Tumor Syndrome (Overlap of Cowden syndrome and the Bannayan-Riley- Ruvalcaba Syndrome): Case Report

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Introduction: PTEN Hamartoma Tumor Syndrome (PHTS) is a rare disease with dominant inheritance characterized by benign (hamartoma) and malignant tumors (breast, endometrium, thyroid). Mutations in the tumor suppressor gene phosphatase and tensin homologue (PTEN) gene are responsible for the etiology.

Objective: In this case report, we present an 11-year-old male who was being monitored due to follicular thyroid cancer, and was diagnosed as PHTS due to accompanying macrocephalus, arterio-venous malformation (hemangioma), hyperpigmented macules on the glans penile and papules on the skin.

Case: The 11-year-old male patient was being followed in our clinic due to follicular thyroid cancer. There was no consanguinity between his parents and no similar medical history in the family. He was investigated due to macrocephaly in antenatal period but the etiology could not be determined. Increasing diameter of thyroid nodule was detected and right lobectomy was performed due to compatible result of the fine needle aspiration biopsy with follicular neoplasms at the age of seven. L-thyroxine treatment was started in the postoperative period because of subclinical hypothyroidism. At the age of nine, magnetic resonance imaging revealed a mass lesion in the thigh (14x6,5cm). The mass removed surgically and pathology was reported as arterio-venous malformation (hemangioma). On physical examination, weight was 39 kg (-0.39 SDS), height was 151 cm (0.35 SDS), head circumference was 60 cm (3.74 SDS) and puberty was consistent with Tanner stage 3. Papules on face, mass lesion (vascular anomaly) of approximately 10x7 cm on the left hip, hyperpigmented macules on the glans penis were observed. Autism findings were not described in the patient whose mental development was usual. The patient had no hyperextensibility and loss of muscle strength. In terms of scoliosis, spine radiography revealed dextroscoliosis. In the clinical observation (11 years of age), multiple nodules (multinodular goiter) were detected in the left thyroid lobe. Molecular genetic analysis for PHTS with the present findings detected c.388C> T heterozygous pathogenic variant in the PTEN gene. Because of the early diagnosis and macular lesion in penis, the patient was concordant to BRRS syndrome; and was overlapped with CS because of thyroid malignancy.

Conclusion: PHTS is rare and its subtypes may not be differentiated. In this report, the 11-year-old patient whose clinical findings concordant with CS and BRRS, was pointed out. PHTS requires multidisciplinary monitoring and approach in terms of endocrine and non-endocrine pathologies.

P1-246

Knowledge of the natural history of paediatric MEN1 is required to inform decision making for predictive testing in childhood

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Background: Multiple Endocrine Neoplasia type 1 (MEN1) is a dominantly inherited syndrome characterised by parathyroid hyperplasia, pancreatic neuroendocrine tumours (PNET) and pituitary adenomas, although >20 tumours are described. Clinical guidelines¹ recommend annual biochemical surveillance and abdominal imaging from <10yrs and pituitary imaging every 3yrs. Age at start of surveillance is derived from the youngest reported patient with an MEN1 manifestation. The commonest paediatric manifestation is hyperparathyroidism, affecting approximately 50% of patients by age 20yrs.

Methods: Retrospective, observational study of paediatric patients screening according to international guidelines¹.

Results: Data from 13 patients diagnosed on predictive testing aged 5-13yrs are presented in Table 1. No patient has required an intervention to date.

Discussion: In our small population, a large number of appointments, MRI scans and biochemical tests were performed and days at school and work were lost. Whether tumour surveillance heightens or reduces anxiety is likely to be highly individual.

Tumour prevalence of MEN1 in childhood is largely unknown. There is likely to be a publication bias, favouring description of patients with tumours. Predictive testing is often undertaken in children too young to give consent. Some adults, diagnosed in childhood, may have elected not to be tested.

Surveillance imaging risks identification of incidental findings of uncertain significance. The natural history and optimal timing of surgery for small, non-functioning PNETs and adrenal tumours is unknown, while the timing of parathyroid surgery is debated.

To enable families to make informed decisions about predictive testing and surveillance, international collaboration is required to generate data describing the prevalence and natural history of MEN1 related tumours in childhood.

Reference

- Thakker R et al. Clinical Practice Guidelines for Multiple Endocrine Neoplasia Type 1 (MEN1), *JCEM* (2012) 97: 9 (1); 2990–3011

Table 1. (for Abstract no FC5.6)

Patient	Age at diagnosis (years)	Number of hospital visits	No of blood tests (prolactin, IGF1, calcium and PTH)	No of MRIs (pituitary and abdominal)	Manifestations of MEN1
1	13	5	4	2	none
2	8	9	6	2	Asymptomatic eucalcaemic hyperparathyroidism
3	5	7	5	2	none
4	11	3	2	3	none
5	13	3	2	3	none
6	10	3	2	3	none
7	12	3	2	3	Asymptomatic eucalcaemic hyperparathyroidism
8	12	2	1	2	none
9	9	11	8	2	Asymptomatic eucalcaemic hyperparathyroidism
10	5	2	1	2	none
11	5	2	1	2	none
12	7	2	1	2	none
13	8	2	1	2	none

One AIRE gene mutation and two different clinical manifestations in a couple of brothers

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Autoimmune polyglandular syndrome type 1 (APS-1) is also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). Clinical manifestations are widely variable. It is an autoimmune disease which is characterized by the triad hypoparathyroidism, Addison disease, and chronic mucocutaneous candidiasis. However, several other autoimmune disorders, not necessarily endocrinological, differing in number and severity, may be present. APS1 is mostly caused by mutations in the autoimmune regulator (AIRE) gene located on chromosome 21q22.

We present the case of two brothers diagnosed with APS-1; molecular analysis revealed a compound heterozygosity for the AIRE gene (c. 415C>T; 967-979 del p r139* L323Sfs* 51 frequently reported in literature) in both. However, they showed very different signs and symptoms at onset.

The older brother was diagnosed at 11 years old after presenting with psoriasis, recurrent mucosal and cutaneous candidiasis since infancy, adrenal insufficiency and hypoparathyroidism. In therapy with rGH for pituitary hypoplasia.

The younger brother presented oral fungal infections and onychomycosis since the very first months of life. At the age of 8 years he showed chronic abdominal pain that led to the finding of hypertransaminasemia.

Workup for hepatitis A, B, C, and Epstein-Barr viruses had yielded no signs of active infection. Anti-gliadin and anti-tissue transglutaminase IgA as well as anti-kidney-liver microsomal and anti-smooth muscle antibodies were negative. A liver biopsy demonstrated severe lympho-histiocytic infiltrate in the portal tracts with moderate interface hepatitis. Treatment with oral prednisone was recently started.

Autoimmune hepatitis is present in 15- 20% of patients with APS-1 and it's rarely the presenting clinical manifestation. Typically, presents with elevated levels of AST and ALT. Treatment requires immunosuppression with the use of glucocorticoids.

As suggested by current literature, clinical APS1 presentation is extremely variable, with poor genotype-phenotype correlation; the two brothers reported show the same genotype, however one of them presented with typical APS-1 triade while the second presented the mucocutaneous candidiasis associated with the extremely rare autoimmune hepatitis.

A novel AIRE gene mutation in two siblings revealing different phenotypes of autoimmune polyendocrine syndrome type 1

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Background: Autoimmune polyendocrine syndrome type 1 (APS-1) is a rare autoimmune disease characterized by chronic mucocutaneous candidiasis, hypoparathyroidism and primary adrenal insufficiency. Minor components of the disease are diverse among patients, even within the same family. APS-1 is autosomal recessively inherited and caused by biallelic mutations in the autoimmune regulator (AIRE) gene.

Objective and hypotheses: To define different clinical and laboratory characteristics of two affected siblings diagnosed as APS-1 with the same genetic cause.

Method and results: Case 1: A 3.7-year-old girl of consanguineous parents was referred due to tetany. She was born with a birth weight of 3300 grams after an uneventful term pregnancy. Physical examination revealed a weight of 13.7 kg (SD score -0.98), height 95.2 cm (SD score -1.23) with normal systemic examination and prepubertal development. She was diagnosed with hypoparathyroidism due to hypocalcemia, hyperphosphatemia and low parathyroid hormone levels. During follow-up, she revealed dental enamel hypoplasia, fragile nails, malabsorptive symptoms and growth retardation. At the age of 12, she was diagnosed with growth hormone deficiency with normal MRI of hypophysis and normal 46,XX karyotype.

Case 2: A 4.2-year-old brother of the index patient presented with hypoparathyroidism. He was born with a birth weight of 3750 grams after an uneventful term pregnancy. Physical examination revealed a weight of 18 kg (SD score +0.35), height 104 cm (SD score -0.32) with normal vital signs and normal prepubertal development. During follow-up he revealed ectodermal dystrophy of the nails and total alopecia areata. Adrenal functions of the both patients were normal. Genetic analysis of AIRE gene in these two siblings revealed a novel homozygous mutation NM_000383.4:c.464-3C>G. The familial segregation was consistent with an autosomal recessive trait.

Conclusion: This is the first report of the mutation NM_000383.4:c.464-3C>G in AIRE gene, which resulted in different phenotypes of APS-1 in two siblings. Here we also report isolated growth hormone deficiency as an unusual finding of APS-1.

Pituitary, Neuroendocrinology and Puberty

P1-249

Use of Desmopressin for Bilateral Inferior Petrosal Sinus Sampling (BIPSS) in Pediatric Patients with Cushing Disease (CD)

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Introduction: BIPSS before and after desmopressin stimulation has been shown to be a useful tool for diagnosis of ACTH-dependent CD and negative magnetic resonance imaging (MRI) or positive MRI but inconsistent biochemical data, in adult patients. However, little is known about its usefulness in pediatric population.

Objective: To evaluate the prevalence of negative MRI, the sensitivity of BIPSS before and after desmopressin stimulation for CD diagnosis and the tumor localization in a pediatric population.

Design: It is a retrospective study. Twenty-three pediatric patients, (10 males), mean age: 12.6 ± 2.5 years (y) (range 5.9–17.3) followed in a single tertiary centre were included. All the patients had hypothalamic pituitary MRI and biochemical diagnosis of CD. In case of negative MRI, patients underwent BIPSS. CD was suspected if inferior petrosal sinus (IPS) to peripheral (P) ACTH ratio was > 2 at baseline and > 3 after desmopressin stimulation. Lateralization was defined if IPS gradient was > 1.4 . Diagnosis of CD was confirmed by surgery and/or clinical evolution.

Results: Seven out of 23 patients had negative MRI (30.4%) and underwent BIPSS, (3 males and 4 females), mean age: 11.6 ± 3 y (range 5.9–14.1). Technical success rate was 100% for bilateral cannulation and no complications were recorded. In all patient baseline IPS/P ratio was > 2 , sensitivity 100%. All but one patient had IPS/P ratio after desmopressin > 3 , sensitivity 85%. Sampling predicted tumor lateralization in 4/7 patients (sensitivity 57%). IPS/P ratio pick was at 3 minutes, except in the patient who did not respond to desmopressin. Only one patient, different from the non responding desmopressin test patient, had persistent disease after surgery.

Conclusion: The prevalence of negative MRI was similar to that described in adult patients. BIPSS basal and after desmopressin was safe and highly sensitive for the diagnosis of CD in this pedi-

atric population. The time of BIPSS after desmopressin might be reduced without affecting the sensitivity. BIPSS was not sensitive enough for the correct lateralization of the pituitary tumor. More data are needed to confirm our results.

P1-250

Correlation between pubertal growth and testicular volume in boys – a longitudinal study

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Background: Few studies have investigated how the pubertal increase in testicular volume (TV) is related to pubertal growth spurt in a longitudinal setting. Increased TV, indicating onset of puberty in boys, mirrors the enhanced testosterone production in the testicles which also give rise to the pubertal growth spurt. The QEPS-growth model makes it possible to conduct detailed analyses of pubertal growth and separate total growth into specific pubertal (P-function) height gain and basal growth (QES-functions)^{1,2}.

Objective: To investigate the relationship between increase in TV in healthy boys with their pubertal growth spurt. To visualize the individual variation in the relation between TV and the attained specific pubertal height gain.

Method: The study group included 31 healthy boys, longitudinally followed during puberty with 1–4 yearly visits, including height measurements and assessments by trained paediatric endocrinologists of testicular volumes (TV), by the method of Prader³. TV during puberty were assessed in median 5 times (range 2–26). Analyses of growth patterns were done with the QEPS-growth model^{1,2} and pubertal heights expressed in both cm and by QEPS-growth estimates, i.e. how many % of the specific P-function-pubertal growth that was attained at each visit. The testicular volume was related to % of the specific P-function-pubertal gain attained (P%).

Results: As expected, there was a high correlation between TV and the specific P-function-pubertal gain ($> 90\%$ explained), and each boy followed his trajectory. However, the individual variation was considerable: at TV 3 ml, median 6%, “P6%”, (range 0.2–24%) of the specific P-function-pubertal growth was reached.

Testicular Vol.	3ml	4ml	6ml	8ml	10ml	12ml	15ml	20ml	25ml
P%, mean	6	14	18	35	40	58	80	95	98
P%, range	0.2-24	2-31	3-48	13-55	16-65	9-86	44-98	62-100	92-100
Visits, n	34	17	13	20	17	21	39	35	10

Mean and range of P%; of specific P-function-pubertal height gain attained at different TV; testicular volumes.

Corresponding values at 4,6,8,10,12,15,20 and 25 ml TV were 14,18,35,40,58,80,95 and 98%, Table:

Conclusion: The specific pubertal gain in height has for the first time been analysed/visualized in relation to TV during puberty. We found a high correlation between TV and specific pubertal height gain, demonstrating the validity of the QEPS-model in this new setting. Each boy followed his trajectory, with broad inter-individual variation in TV vs P%, of the specific P-function-pubertal height gain.

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P1-251

Central diabetes insipidus in children: role of GH antibodies

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Central diabetes insipidus (CDI) in children is caused by brain tumors, Langerhans cell histiocytosis (LCH), trauma, infections, or genetic abnormalities in about 60% of the cases. In the remaining 40%, CDI is idiopathic even after detailed clinical and radiological investigations. Aim of the study was to assess whether measurement of serum antibodies against human growth hormone (GH) could aid in the identification of the etiological factors for CDI.

We followed 65 children with a diagnosis of CDI established at a single centre (Gaslini Hospital, Genoa, Italy) between March 2000 and May 2018. Of them, 36 were females and 29 males. Their diagnosis upon detailed clinical and morphological follow up was idiopathic (No.=31), brain tumor (No.=24), LCH (No.=6), genetic defects (No.=3), or pituitary abscess (No.=1). The median age at diagnosis and median follow up time were 8.9 and 8.5 years, respectively. Brain MRI and studies of anterior pituitary functions were performed in all patients at baseline and on follow up. Serum antibodies against native human GH were measured by a in-house ELISA assay where values below 50arbitrary units per mL are considered negative. In 8 children two serum collections were available and in 4 three, for a total of 81 sera.

Age at diagnosis was significantly higher in patients with brain tumor. Anterior pituitary hormone defects were more frequent in patients with LCH even before specific treatment began($p=0.008$).

while the association between anterior defects and tumors was significant only after treatment (surgery, radiation or chemotherapy). Patient with normal pituitary stalk at disease onset were more likely to develop GH deficiency during follow up($p=0.043$). The median nGH antibody levels were overall similar in the 5 diagnostic categories, being in all cases<50 AU/mL. Interestingly, however, very high GH antibody levels(>200) were seen only in patients with idiopathic CDI. When sequential sera were available, GH antibodies decreased over time. GH antibodies were higher in patients without pituitary stalk thickening ($p=0.032$), and did not differ according to gender, age at diagnosis, age at time of blood test, disease duration, treatment type, or anterior pituitary hormone defect.

The study confirms the challenge of discovering new etiologic factors in idiopathic CDI, as well as identifying factors that predict a specific etiology. GH antibodies do not seem to associate with specific CDI etiologies, although the highest levels observed in the idiopathic form suggest autoimmunity as a possible contributor to the pathogenesis of this condition.

P1-252

Brain Malformations and Sellar Spine as possible causes of Central Precocious Puberty in a large monocentric study

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Background: Central precocious puberty (CPP) is defined as the secondary sexual characteristics onset before 8 years of age in females and before 9 in males, due to premature activation of the hypothalamic-pituitary-gonadal axis. The underlying cause remains idiopathic in the great majority; based on the 2009 Consensus, 2% to 7% of girls who have onset of CPP between the ages of 6 and 8 years have unsuspected pathology and only 1% have a tumor such as a glioma or astrocytoma. Aim of our retrospective study was to assess the anthropometric, biochemical and MRI characteristics at presentation of a large monocentric cohort of children with CPP.

Methods: Among 160 patients presenting with CPP between November 2009 - April 2019, we analyzed retrospectively the preliminary data of 120 children, including anthropometric measures at the start of GnRH agonist therapy, FSH and LH levels before and after a GnRH test and brain MRI.

Results: All patients were evaluated (n=16 males-M, 13.3%, n=204 females-F) at a mean age of 7.8 ± 1.6 yrs. Thirty-two patients (26.6%; n=25, 24% F and n=7, 43.8% M) displayed neuroimaging abnormalities: n=17 (14.1%; n=5M, n=12F) brain malformations (BM) such as corpus callosum hypoplasia, Rathke Cist, Arnold Chiari type 1 etc; n=6 (5%; n=1M, n=5F) Hamartomas (HA); n=4F (3.3%) brain tumors (BT) (n=2 gliomas, n=1 astrocytoma, n=1 Langerhans cell Histiocytosis). In 6 patients (5%; 1M, 5F) a sellar

spine (SSP) was detected. MRI was normal (iPP) in 88 subjects (73.3%; n=9, 56.2% M and 79, 75.9% F).

At diagnosis F and M did not differ for age at treatment, height SDS, BMI SDS, puberal stage, baseline FSH and LH and peak FSH and LH after GnRH testing. iPP, BM, HA, BT and SPP patients did not differ for any anthropometric measures at the start of GnRH agonist therapy, FSH and LH levels before and after a GnRH test in the entire cohort. MRI abnormalities increased up to 34.6, 32.3 and 32.5% of patients evaluated before 5 yrs, 6 yrs or 7 yrs of age, respectively.

Conclusions: brain malformations and sellar spine represent other potential causes of CPP, either in females and in males; in particular, sellar spine, a bony spur protruding from the central portion of the dorsum sellae, may be a not negligible potential cause of CPP due to deformation of the growing pituitary gland.

P1-253

Changes in the body mass index in children with Central Precocious Puberty' under gonadotropin-releasing hormone analogue treatment - a multicentric study

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Precocious Puberty is defined by the onset of pubertal development at an age 2-2.5 standard deviations earlier than the normal population. Central Precocious Puberty (CPP) is diagnosed when the hypothalamic-pituitary axis is activated. Gonadotropin-releasing hormone analogues (Gn-RH analogues) are the main treatment option, but sometimes controversial. Whether this treatment influences children's body mass index (BMI) and a different BMI progression is still unclear.

Aims: To evaluate the effect of Gn-RH analogues on the BMI of children (boys and girls) with CPP at the end and one year after treatment.

Methods: Cross-sectional and multicentric study from a National Standardized Digital Database, enrolled from eleven Pediatric Endocrine Departments in Portugal. Five years data collection was analyzed (January 2013 to December 2017). Statistical analysis was performed using SPSS™ 23.0 version. Patients were evaluated before, at the end and one year after Gn-RH analogues' treatment and divided into four groups according to their BMI

standard deviation score (BMI-SDS): low weight (LW), normal weight (NW), overweight (OW) and obesity (OB).

Results: A total of 241 cases presented CPP (90.5% female) and 17.4% were under 6 years of age. Only the ones that undergone treatment with Gn-RH analogues were analysed (84%); from these 46.5% (n=94) concluded the treatment when normal puberty was attained and 32% (n=65) continued to be followed one year after. At diagnosis of CPP, 44.7% of the patients were NW; from these, 33.4% became OW/OB after treatment with Gn-RH analogues. This occurred for 35% (p<0.001) of the NW girls' but this association was not significant for boys. A positive association between Gn-RH analogues and the prevalence of OW and OB (p<0.01) was found. Patients treated with monthly triptorelin were significantly more OW/OB compared to those on depot triptorelin (45.5% versus 29%, p<0.001). One year after treatment, 91.3% of the patients with NW remained with a similar weight. Moreover 25% of the patients that became OW/OB with Gn-RH analogues, returned to NW again (p<0.001).

Conclusions: The authors concluded that treatment of PPC with Gn-RH analogues, especially monthly triptorelin, increases BMI in girls but not in boys. A significant percentage of patients, however returns to a NW status one year after treatment. We suggest that CPP treatment modality should be individualized according to BMI progression.

P1-254

A novel approach for the evaluation of hypothalamic-pituitary region in patients with growth hormone deficiency: Pons ratio

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Objective: In patients with growth hormone deficiency (GHD), even in those with no major organic lesion, anterior pituitary height (APH) is reported decreased. Limitations in the evaluation of APH and changes according to pubertal status make its validity questionable. Recently, in a small scale study, pons ratio (PR) has been suggested as a more sensitive marker for evaluation of pituitary gland in GHD patients. The study aims to evaluate the validity of PR as a diagnostic tool in GHD.

Method: We retrospectively evaluated the pituitary MRI of patients with a diagnosis of GHD. Primary axis(PA) was assigned as a line crossing the midsaggital dorsum sella and fourth ventricle which divides pons into two symmetrical parts. PR was defined as the pons height above the PA divided by total pons height. The PR of patients with GHD was compared with patients with no GHD.

Results: Study included 138 patients with GHD (84 male) and 28 healthy controls. While 127 patients (92%) had isolated GHD, 11 (8%) had multiple pituitary hormone deficiencies (MPHD). In the isolated GHD group, 18 patients (14.2%) had an organic lesion on pituitary MRI. The PR measured for GHD patients (mean: 0.32 ± 0.90 ; range: 0.15-0.63) was higher compared to those of the control subjects (mean: 0.27 ± 0.63 ; range: 0.19-0.44) ($p=0.005$). There was a statistically significant moderate negative correlation between PR and pituitary height ($r=-0.273$; $p=0.002$). The PR of GHD patients who had an organic brain lesion (mean: 0.37 ± 10 ; range: 0.15-0.55) was higher than those with no organic lesion (mean: 0.32 ± 0.86 ; range: 0.17-0.63) ($p=0.016$). ROC analysis revealed the best cut-off value of PR as 0.27 for GHD with a sensitivity of 71% and specificity of 53%. In addition, bone age, peak GH value in the GH stimulation test and IGF1-SDS was negatively correlated with PR with $r=-0.375$ ($p=0.000$), $r=-0.246$ ($p=0.005$) and $r=-0.281$ ($p=0.003$) respectively. Although the pituitary height was higher in pubertal subjects compared to the prepubertal group, there was not a statistically significant difference between the PR of prepubertal and pubertal patients.

Conclusion: As is not change depending on pubertal status, PR can potentially be a more sensitive tool for evaluation pituitary gland in GHD patients compared to APH. PR measurement is a noninvasive, practical and cost-benefit method that can be measured using a sagittal section of routine pituitary MRI.

P1-255

Effects of 5-Hydroxymethylfurfural on Pubertal Development of Wistar Rats

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Introduction: 5-Hydroxymethylfurfural (HMF) is formed when sugars like glucose and fructose are heated in the presence of amino acids. HMF is naturally present in many foods and we are exposed to HMF in daily life. There are conflicting data on potential genotoxic, mutagenic, carcinogenic, DNA-damaging, organotoxic and enzyme inhibitory effects of HMF and its metabolites. We aimed to investigate toxic effects of HMF on reproductive system in peripubertal rats.

Methods: In the study, 24 immature Wistar rats were divided into control and HMF groups fed 750 mg/kg/day and 1500 mg/kg/day for 3 weeks from postnatal day 21. They were controlled for vaginal opening (VO) daily and necropsied on postnatal day

44. Blood samples were collected with cardiac puncture on termination day. Follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone (P) and anti-Müllerian hormone (AMH) levels in blood serum were measured using rat-specific enzyme-linked immunosorbent assay kits. Hormone levels, reproductive organ weights and ovarian follicle counts were compared.

Results: High dose HMF group had earlier VO with higher LH and E2 levels. High dose HMF group also had increased number of secondary atrophic follicles and decreased AMH levels.

Conclusion: These results indicate that peripubertal exposure to HMF in high doses result in precocious puberty and decreased ovarian reserve in Wistar rats.

P1-256

Kisspeptin levels is a new diagnostic approach of hypogonadotropic hypogonadism in boys

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Background: In hypogonadotropic hypogonadism (HH), hypophyseal follicle-stimulating and luteinizing hormones, normally released with GnRH stimulation, are detected low. Since kisspeptin (KP) is a strong stimulant of GnRH neurons, it is considered to have a role in HH aetiology. It may be hypothesized that abnormal plasma levels of KP are indicative of HH.

Aim: Evaluation and comparison of plasma KP levels in boys of pre-pubertal age, with normal puberty and diagnosed HH.

Results: The study comprised 22 boys with HH (median age 14, range 14-17 years), 25 boys with normal puberty (median age 16, range 14-18 years), and 28 pre-pubertal boys (median age 6, range 3-10 years). Statistically significant difference was found for the overall distribution of the plasma KP values across different groups (Kruskal-Wallis $H = 21.95$, $p < 0.001$). The highest values were found in the HH group (median: 45.0 pg/mL, range: 13.1-471.6 pg/mL). Median value in the pre-pubertal boy was equal to 13.8 pg/mL (range: 13.2 - 82.5 pg/mL), median value in normal pubertal adolescents was equal to 13.8 pg/mL (range: 13.1 - 37.2 pg/mL). ROC curve analysis was performed. The area under the ROC curve (AUC) was equal to 0.854 (95% CI: 0.720 to 0.940), enabling rejection of the null-hypothesis (area of 0.5) ($p < 0.0001$). The criterion value that ensured optimal balance between sensitivity and specificity was equal to 16.9 pg/mL. This corresponds to the value of the Youden index J equal to 0.6473, test sensitivity equal to 72.73, and test specificity equal to 92.0. Plasma KP level exceeding 16.9 pg/mL was a reliable predictor of HH (sensitivity = 72.73, specificity = 92.0).

Conclusion: Plasma KP levels are elevated in HH cases and may serve as a useful diagnostic tool in evaluating boys with HH.

P1-257**Fetal and post-natal growth are impaired in children with deletions of the *GH1* gene: description of a cohort of 14 patients**

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Data on the birth parameters of patients with growth hormone deficiency are contradictory; recent studies suggest that congenital growth hormone deficiency is associated with impaired fetal growth. The main objective of this study was to describe the birth parameters of children with GH-1 gene deletion.

This study included 13 patients (of 10 families) for whom a homozygous (or compound heterozygous) deletion of the entire *GH1* gene has been identified, and an additional patient with a deletion of the entire *GH1* gene and a deletion of one nucleotide (leading to a frameshift) on the second allele.

Age at diagnosis was from 7 months to 14 years, with a mean height at the time of diagnosis at -7.1 +/- 1.9 SDS. Among the eleven children with an available birth length, mean birth length was -2.4 +/- 0.7 SDS, ranging from 45 to 49 cm, and six had birth length < -2 SDS. Birth weight was normal (-0.4 +/- 1.1 SDS). The mean genetic target height was -1.1 +/- 0.6 SDS. Twelve of the fourteen patients received exogenous GH treatment. In seven of them, the GH treatment allowed a catch-up of growth with a final height close to the target height. The mean final height was -3.26 +/- 1.8 SDS for the whole cohort. For three patients, anti-GH antibodies were detected.

This study reports a large cohort of patients with *GH1* deletions. Our results support the hypothesis that GH acts on fetal growth, as children with deletion of the *GH1* gene had growth retardation at birth, which worsens after birth.

P1-258**Novel pubertal references for girls using ultrasound to stage breast development. The Bergen Growth Study 2**

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Background: Using ultrasound to examine the glandular breast tissue is a promising method for staging pubertal breast development. However, breast ultrasound for this purpose has not been explored in a large sample of healthy girls in different developmental stages, and normative data have been unavailable.

Objective: To present novel pubertal references for breast ultrasound stages, Tanner breast (B) and pubic hair (PH) stages, and menarche for girls living in Norway.

Materials and Methods: A cross-sectional sample of 703 girls (6.1-16.2 years) living in Bergen, Norway, were measured and included into the study (Bergen Growth study 2) in 2016-17. All girls were examined with ultrasound to determine the pubertal breast developmental stage (USB). Tanner B and PH stages were assessed clinically. The girls were also asked about menarche. Ages at entering USB, Tanner B and PH pubertal stages 2-5, and menarche were estimated using a generalized linear and a generalized additive models. Pubertal breast staging with USB and Tanner B were compared using kappa statistics with linear weights and Spearman's correlation.

Results: Median age (p3, p97) at onset of breast development was 10.2 (7.81, 12.62) years for USB 2, and 10.38 (8.18, 12.58) for Tanner B2. For PH2 and menarche, estimated median ages at onset were 10.88 (8.61, 13.15) and 12.67 (11.04, 15.88) years, respectively. Significant correlation was found between USB and Tanner B breast development stages ($r=0.95$, $p<0.001$), and were in very good agreement (kappa 0.87; 95% confidence interval: 0.85, 0.88).

Conclusion: Staging of pubertal breast development done with ultrasound provided similar ages at pubertal onset compared to traditional Tanner B staging. The estimated ages at onset of breast development, PH and menarche in our study are in accordance with recent European studies.

P1-259

Disruption of Hypothalamic regulation of Appetite associated with Proton Beam Therapy

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Introduction: Proton beam therapy (PBT) is being used increasingly for craniopharyngioma, as it is perceived to be a major benefit. There are some limited data relating to endocrine dysfunction following PBT, but very limited data on hypothalamic disturbance. Here we report two patients who presented with hypothalamic disruption immediately following PBT for craniopharyngioma.

Case 1: A 12 year old girl presented with seizure. MRI revealed obstructive hydrocephalus and suprasellar tumor. At surgery hydrocephalus was drained and ommaya reservoir inserted. Tumour biopsy confirmed craniopharyngioma. A near total resection was performed (minimal residual tumor adherent to the posterior cerebral artery and hypothalamus). She developed multiple pituitary hormone deficits (MPHD) post near total resection and was started on thyroxine, hydrocortisone, desmopressin and later growth hormone. Four months post-surgery, she received PBT. Immediately following PBT she became anorexic with fall in BMI of 4 SD over 8 weeks. (Table 1)

Case 2: A suprasellar tumor was identified on routine MRI at diagnosis of growth hormone deficiency in a 4 year old male. Four months following partial resection (small layer of residual tumour at pituitary stalk and base of hypothalamus) MRI revealed growth

of a moderate-size cyst above residual lesion. The Child developed MPHD post second surgery requiring thyroxine, hydrocortisone and growth hormone. Eleven months post second surgery (cyst fenestration and insertion of ommaya reservoir) he received PBT which was followed by abrupt onset of anorexia (BMI = 2SD) requiring supported nutrition by gastrostomy. Following sustained weight gain and recovery of appetite 1 year post PBT, gastrostomy was removed.

Conclusion: Although PBT is generally well-tolerated for the treatment for craniopharyngioma; long-term follow up and larger cohort studies are necessary to establish whether dosimetric advantages of PBT translates to clinical benefits in improving long-term toxicities.

P1-260

A case-control study of exposure to bisphenol-A and phthalates in girls with early onset of puberty

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Background: Over the past several decades, the age of pubertal onset in girls has shifted downward worldwide. Several factors including genetic predisposition, psychosocial and socio-economic conditions, diet and ethnicity may have contributed to this phenomenon. Epidemiological and animal studies have shown that the exposure to BPA and DEHP may be associated with early onset of puberty in girls.

Objective: To investigate the association between the exposure to BPA, DEHP's metabolites in girls with idiopathic premature thelarche (IPT) or idiopathic central precocious puberty (ICPP).

Table 1: Serial weight and body mass index (BMI) of both patients

Related procedure	Case 1		Case 2	
	Weight in Kg (SD)	BMI (SD)	Weight in Kg (SD)	BMI (SD)
Before 1 st Surgery	45.7 (0.64)	23.0 (1.58)	16.6 (0)	19.7 (2.93)
Before 2 nd Surgery	47 (0.55)	22.8 (1.47)	16.2 (-0.48)	17.8 (1.76)
Before PBT	40.6 (-0.27)	19.7 (0.52)	14.6 (-1.72)	14.6 (-0.53)
On admission (after ≈ 8 weeks of PBT)	26.6 (-2.11)	13.0(-3.47)	13.4 (-2.56)	13.2 (-1.83)
After 1 Year	37.5 (-1.5)	18.0(-0.61)	21.1 (0.03)	17.6 (1.44)
After 2 Year	58.6 (0.45)	27.3(1.89)		
After 3 Year	63.9 (0.82)	26.9(1.66)		
Recent weight	76.9 (2.07)	30.2 (2.11)	26 (0.94 SD)	18.7(1.80)

Methods: A case-control study was conducted in 97 girls, subdivided into 3 groups: 31 with ICPP (mean age 7.3 ± 0.07), 39 with IPT (mean age 6.56 ± 1.6) and 27 controls (mean age 6.67 ± 2.3).

Urine BPA and DEHP metabolites were measured by gas chromatography and high-performance liquid chromatography (LC-MS/MS). Metabolic and hormone levels were assessed. Individual environmental exposure was evaluated through "ad hoc" questionnaires providing data on life styles, diet and other potential determinants of exposure.

Results: Our findings showed the presence of measurable concentrations of the EDCs in all girls, including the control group. These data demonstrate the widespread exposure to these compounds. ICPP and IPT girls showed no significantly difference in EDCs levels neither compared to controls nor compared to each other. In IPT group, a significant positive correlation between DEHP levels and FSH peak was found, suggesting that phthalates could potentially cause self-limited breast development without progression to true ICPP ($p < 0.05$). Furthermore, in IPT group significant negative correlations were found between DEHP metabolites, KISS serum levels and AMH hormone ($r = -0.4$, $p = 0.01$; $r = -0.37$, $p = 0.02$, respectively). Since no significant difference in the exposure was found between cases and controls, we considered that the association between life style data derived from questionnaires and exposure corresponded to data from general pediatric population. Briefly, higher levels of phthalates were associated with: i) use of disposable plastic; ii) use of plastic containers in microwave; iii) playing many hours a day with plastic toys including electronic toys. The use of disposable plastic was also associated with higher levels of BPA.

Conclusions: Our findings suggest that concentrations of urine BPA and DEHP's metabolites are measurable in all girls. The use of plastic exposes girls to a higher contamination from both BPA and DEHP. These results warrant further experimental and prospective clinical investigations to clarify the potential role of EDCs in modulating the timing of puberty in girls.

Sex Differentiation, Gonads and Gynaecology or Sex Endocrinology

P1-261

Long-term urological and psychosexual outcome of men born with hypospadias

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Introduction: According to EAU's guidelines, hypospadias (HS) repair is best performed between 6 and 18 months of age. Little is known about the long-term patient satisfaction or urological outcome following HS surgery.

Aims: To examine the psychosexual and urological outcome of young adult men (16-21 years old) born with all forms of non-syndromic HS as compared to healthy controls, as well as patient and parental satisfaction following HS surgery.

Methodology: Cross-sectional assessment in Ghent University Hospital and Vienna Medical University. Participants filled in five questionnaires: the Decision Regret Scale (DRS), Penile Perception Score, Sexual Quality of Life – Male, International Index of Erectile Function and a custom-made questionnaire. The DRS and custom-made questionnaires were also completed by the participants' parents. Urological examinations included: uroflow, post-micturition and testicular ultrasound and genital examination. IBM SPSS[®] 25.0 was used to analyze the data: using a Pearson correlation, unpaired student t-test, Mann Whitney-U test or chi-square test, as appropriate.

Results: Results are presented in Table 1.

Table 1: Summary of results

1. Questionnaires		
Custom parents	Shocked by HS: at birth 95/150 (63,3%) - on the long-term: 19/150 (12,7%) Worries about testicular function: 71/150 (distal: 45,7%; prox: 51,1%)	
Custom participants	Regretted that their parents decided for them on having the HS repair: 3/153 (2,0%) Wished they never had the repair: 2/153 (1,3%)	
DRS	HS: $\rho=0,222$, $p<0,001$	Parents: $\rho=0,291$, $p<0,001$
Regret correlation with reintervention		
PPS	HS: 13/153 (8,5%)	Controls: 1/42 (2,4%)
Dissatisfied about genital appearance		
SQoL-M	HS: 1/153 (0,7%)	Controls: none
Sexual dysfunction (< 50%)		
IIEF-5	HS: 10/83 (12%)	Controls: 2/33 (6,1%)
Erectile dysfunction (< 21)		
1. Urological		
Suboptimal esthetic outcome	Distal: 16/108 (14,8%)	Prox: 16/45 (35,5%)
Varicocele grade II or higher	HS: 31/153 HS (20,3%)	Controls: 2/42 (4,8%)
Abnormal uroflow	Plateau HS: 34/149 (22,8%) Distal: 21,9%; Prox: 25,0%	Staccato HS: 2/149 (1,3%) Distal: 5/103 (4,9%) Prox: 2/45 (4,4%)
Testicular ultrasound	Microlithiasis ($p=0,777$) HS: 13/153 (8,5%) Controls: 3/42 (7,1%)	Mean volume HS/controls Right: 12,3mL/12,7mL, $p=0,547$ Left: 11,9mL/12,1mL, $p=0,740$ Mean volume Complex/isolated HS Right: 9,5mL/12,6mL $p=0,002$ Left: 7,9mL/12,3mL $p<0,001$

Conclusion: Very few patients regret having had HS surgery in childhood. Patients and physicians value outcome of HS surgery according to different criteria. We found a high rate of varicocele post HS surgery of unclear origin so far. Our data highlight the need for postpubertal revision of HS cases as long-term complications may occur that require surgical intervention at some times. In some cases, psychosexual counseling may be recommended.

P1-262

Long-Term Outcome In Leydig Cell Hypoplasia

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Background: Leydig Cell Hypoplasia (LCH) is a very rare autosomal recessive condition that is manifested by a wide spectrum of phenotypes, ranging from completely female external genitalia to male genitalia. Long-term outcome in these patients is unclear.

Objectives: To assess sex assignment, clinical characteristics and long-term outcome of 46,XY LCH cases.

Patients and Methods: Through the I-DSD registry and its users, clinical information on first and last presentation was gathered on 17 cases of 46,XY LCH born before 2004. A questionnaire was sent to each clinician at these centres to collect information on long-term health. The diagnosis was reached through clinical biochemistry in all and confirmed by genetics in 13 cases.

Results: The median age at the time of first presentation and last assessment was 17 years (range 8 days, 45 years) and 22.8 years (7.7, 62), respectively. Current gender was male in 4 (23%) and female in 13 (77%); two cases were reassigned, one from female to male at 5.3 years and the other from male to female at 17 years. Median EMS, out of 12, at first presentation was 5 (5, 6) and 2 (1, 5) in cases raised as male and female, respectively. All cases had surgery: median age at last repair of hypospadias in males was 5.8 years (2, 8.4); median age at bilateral gonadectomy in the females was 17.9 years (2.2, 46). Cases raised as males were likely to experience more surgical interventions with a median number of hypospadias repairs of 2 (1-4). At last presentation, undermasculinisation was observed in all 4 males with median EMS of 9 (6-9); all of them had micropenis, 2 (50%) had delayed puberty and one also had low testicular volume and hypospadias. All male cases had low testosterone levels despite elevated gonadotrophins. Among the 13 females, 11 (85%) required oestrogens to induce secondary sex characteristics. Of the 17 cases, DXA was performed in 8 (47%) and 7 (88%) of these cases exhibited osteopenia/osteoporosis. One male had azoospermia and 2 obese females developed metabolic syndrome.

Conclusion: Children with LCH can present with a variable level of undermasculinisation and are more likely to be raised as females. However, irrespective of the sex assignment, there is ongoing evidence of hypogonadism and co-morbidities in young adulthood. A standardised approach to management and monitoring clinical outcomes is required.

P1-263

Clinical and Molecular Characteristics, Genotype-Phenotype Correlation in 113 Chinese Children with SRD5A2 Gene Mutations

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Objective: Studies on 5α-reductase type 2 deficiency (5α-RD) are limited and the genotype-phenotype correlation has not been elucidated. The aim of the study was to analyze clinical and molecular characteristics, genotype-phenotype correlation in a large Chinese 5α-RD cohort.

Design: Database registration study.

Method: We analyzed clinical and genetic data of gene confirmed 5α-RD Children, comparing their phenotypes by using external masculinization score (EMS), the position of urethral meatus and gonads as well as penis length-standard deviation score (PL-SDS).

Results: 85.84% of patients presented hypospadias while 14.16% had normal urethral meatus. When the cut-off value of stimulated T/DHT was 10 or 15, 98.48% and 92.42% of patients were diagnosed respectively. 8 patients with isolated micropenis were diagnosed as 5α-RD by higher T/DHT ratio and *SRD5A2* gene mutations. There was no significant correlation between T/DHT and phenotypes ($p>0.05$). We identified 31 different variants including 10 unreported ones. The p.R227Q was the most prevalent variant (38.50%). The phenotypic indicators of patients with p.R227Q were higher than those without the mutation in multiple comparisons ($p<0.05$). Patients with the homozygous p.R227Q had milder phenotypes and larger standard deviation of phenotypic scores than those with other homozygotes.

Conclusions: Subjects with 5α-RD can present isolated micro-penis and T/DHT cannot foretell the severity of phenotypes. As a founder mutation in Chinese, the p.R227Q seems to link to relatively milder phenotypes and greater phenotypic variability. Variants can explain, at least partially, the heterogeneity of phenotypes, while other factors may also contribute to the phenotypes.

P1-264

Regulation of CBX2 transcription in human development

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Background: The process of sexual differentiation is critical for reproduction in nearly all metazoan. Defects in any of the genes involved in either testicular or ovarian development can result in disorders of sex development (DSD). CBX2/M33 is a chromatin modifier that plays an important role in sexual development and its disorders, highlighted by the fact that M33-deficient mice have male-to-female sex reversal and loss-of-function of CBX2 causes 46, XY DSD in humans. The promoter of CBX2 is unknown; however, there are hints of differential expression by its multiple isoforms across different cell lines and tissues.

Here we aim to characterize the CBX2 promoter in applicable cell lines using a custom reporter construct, to identify a regulatory network in gonadal development in which CBX2 takes part.

Methods: To locate the CBX2 promoter, based on predicted binding sites two candidate regions targeting transcription and one the start of translation, were cloned into the promoterless pGL4.17 Vector upstream of the luciferase reporter gene *luc2*. The constructs were transfected in several cell lines (Cos-1, HeLa, KGN, and NT2-D1), with reporter activity established by performing a dual-reporter assay measuring firefly and *Renilla* luciferases. Dissection of the CBX2 promoter is done to determine essential transcription factor binding sites and investigate DNase I hyper-

sensitive sites, along with related histone activity. Subsequently, ovarian, testicular and adrenal cell lines (KGN, NT2D-1, and NCI-H295R cells respectively) are challenged with the identified regulatory elements to determine the regulation of CBX2 expression.

Results: Utilizing the dual-reporter assay system, we identified an optimal candidate CBX2 promoter construct (-479/+34) that exhibited a significant normalized fold change in activity across several cell lines tested (range from 3.6 – 14.65 fold) when compared to a negative control ($p<0.0074$ – $p<0.0001$). Preliminary results indicate substantial differences in transactivation potential among the various cells, allowing us the potential application of the promoter construct to explore and elucidate differential transactivation of CBX2 in cell models recapitulating ovaries, testis and adrenal cells.

Conclusion: The characterization of a candidate CBX2 promoter could provide insight into the functional role of CBX2 as transactivator, distinct from its known function as chromatin-modifier. Further study of the impact of CBX2 activation and suppression may shed light on potential pathological mechanisms involved in DSD, and ultimately its diagnosis and management.

P1-265

Dynamics in blood pressure after pubertal suppression with GnRH analogs followed by testosterone treatment in male adolescents

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Background: In 2017, the Endocrine Society published guidelines for the endocrine treatment of gender dysphoria/ gender incongruence. Adolescents who meet diagnostic criteria for gender dysphoria undergo pubertal suppression using gonadotropin-releasing hormone analogs (GnRHa) and induction of puberty with gender-affirming hormonal therapy. Blood pressure (BP) monitoring prior to and during treatment with GnRHa in transgender adolescents is recommended. This recommendation is based on a few case reports of arterial hypertension as an adverse effect in girls treated with GnRHa for precocious puberty. There is no published data in transgender adolescents to support the recommendation to monitor BP.

Objective: To examine BP changes in transgender male adolescents treated with GnRHa and after the addition of testosterone treatment.

Methods: Retrospective, single-center, observational study from the Israeli Pediatric Gender Dysphoria Clinic. Included in the analysis were all consecutive transgender male adolescents who were treated solely with GnRHa for at least 2 months. Data extracted from medical records included vital signs, anthropometric measurements, and hormonal levels (LH, FSH, estradiol and testosterone). Outcome measures: systolic and diastolic BP percentiles at baseline, after GnRHa and after testosterone treatment.

Results: 15 transgender males, mean age at baseline was 14.4 ± 1.0 years and Tanner 5 stage of puberty (13 subjects). GnRHa was administered for a mean period of 3 ± 1 months. Testosterone treatment, in 9 transgender males was added at a mean age of 15.5 ± 0.9 years. Diastolic BP (DBP) percentiles increased significantly after GnRHa treatment (from 55.9 ± 26.4 to 73.6 ± 9.4 , $P = 0.019$); the increase in DBP remained significant after adjusting for the change in BMI standard deviation score ($P = 0.047$). BP levels were within the normal range and did not meet criteria for pediatric hypertension. DBP percentiles decreased significantly after adding testosterone therapy (from 72.8 ± 10.1 to 56.0 ± 17.5 , $P = 0.033$), only after adjusting for the change in BMI SDS. Systolic BP percentiles did not change significantly during both stages of treatment. No significant correlations were found between BP percentiles and LH and FSH levels.

Conclusion: Our preliminary findings suggest that pubertal suppression with GnRHa increases DBP in transgender male adolescents and that induction of puberty with gender-affirming testosterone treatment restores DBP percentiles. Further studies with larger cohorts are needed to elucidate the effect of BP dynamics in gender dysphoric adolescents on the metabolic and cardiovascular consequences in young adulthood.

P1-266

A Nationwide Study Of The Prevalence & Initial Management Of Atypical Genitalia & Delayed Sex Assignment In The Newborn

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Background: The prevalence of atypical genitalia and the time taken to assign sex in such cases remains unclear. Provision of optimum healthcare during this period requires a clear understanding of the occurrence of atypical genitalia.

Methods: Prospective electronic survey of clinical members of managed clinical networks in Scotland between 2013 and 2018 seeking notification of term neonates requiring specialist input for atypical genitalia and who were then followed up to the age of 3 months. Cross-verification of the notification process was performed through regional genetics laboratories using karyotype as a surrogate marker to identify additional newborns with atypical genitalia.

Results: 81 neonates who satisfied the reporting criteria were identified through the clinicians and the laboratories providing a birth prevalence of 1 in 3,378 term births in Scotland that

received specialist input for atypical genitalia. Of the 77 cases that completed the 3 month follow up, 49 (64%) presented within 24 hours of birth. Age at presentation ranged from birth to 28 days. Although the age at sex assignment ranged from birth to 14 days, in 51 of 77 infants (66%), sex assignment occurred at birth. Only 1 case was re-assigned and had a different sex at 3 months. Of the 59 infants with a karyotype with a Y-chromosome, 55 (93%) were assigned a male sex and the remainder female. During the first three months, specialist input from a neonatologist or a pediatrician, endocrinologist, surgeon and psychologist was reported in 74 (96%), 58 (75%), 50 (65%) and 9 (12%), respectively.

Conclusions: Atypical genitalia requiring specialist input within the first month of life is rare in term newborns and in only a third of these cases, sex assignment is delayed beyond birth. This study provides new clinical benchmarks for comparing and improving the delivery of care in centers that manage these complex conditions.

P1-267

Endocrine profiling and association with ultrasound measured testicular volume and biometrics in a cohort of Norwegian boys

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Introduction: Male puberty is initiated by endocrine signaling in the hypothalamic-pituitary axis whereby follicle-stimulating hormone (FSH) and luteinizing hormone (LH) enable testicular maturation and synthesis of testosterone. Recent publications have eluded to overnutrition and obesity as relevant factors that may accelerate the timing of puberty. Attainment of testicular volume (TV) 4 ml measured by Prader orchidometer remains the definition of male puberty onset. We recently established ultrasound references for testicular growth as an objective alternative to orchidometry.

Objectives: (i) Model endocrine profiles with reference to ultrasound-determined testicular growth throughout puberty and (ii) determine associations between hormones and standard deviation (SD) scores for body mass index (BMI), weight, waist circumference (WC) and subscapularis skinfold (SSF).

Methods: Testicular ultrasound, bioimpedance, biometric assessments and blood collection was conducted in a cross-sectional cohort of 417 healthy Norwegian boys, age 6-16 years. Circulating levels of testosterone were quantified by liquid chromatography tandem-mass spectrometry (LC-MS/MS). Sex hormone-binding globulin (SHBG), FSH and LH were analyzed using IMMULITE 2000 xpi.

Results: Hormone levels plotted against testicular growth aligned well with TV 4 ml marking the start of testosterone production. TV 4 ml also corresponded to the peak LH/testosterone ratio, a marker of Leydig cell function. Dimension reduction of all serum hormone levels into an endocrine profile principle component was able to predict puberty transition at TV \geq 4 ml (receiver operating characteristic AUC = 0.88, p<0.001). For pubertal boys with TV \geq 4 ml, individual hormones exhibited no correlation with SD scores for testicular growth. For pubertal boys we observed significant inverse Spearman correlations between serum levels of SHBG and SD scores for BMI ($r = -0.31$, p<0.001), WC ($r = -0.24$, p<0.01), weight ($r = -0.29$, p<0.01) and SSF ($r = -0.24$, p<0.01). For BMI and weight SD scores, significant positive correlations persisted with respect to calculated free testosterone index. Circulating total testosterone correlated inversely with body fat percentage ($r = -0.32$, p<0.001) and positively with body muscle percentage ($r = 0.33$, p<0.001).

Conclusion: Ultrasound-determined TV and endocrine status are markers of male puberty onset and progression. Our endocrine model with respect to TV supports the current definition of male puberty onset at TV 4 ml. Our data show significant correlations between free testosterone and SD scores for BMI and weight, suggesting that overweight and obesity may accelerate pubertal development.

P1-268

Idiopathic scoliosis in girls with central precocious puberty: Incidence and effect of gonadotropin-releasing hormone agonists

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Adolescent idiopathic scoliosis (AIS) is the most common form of scoliosis, affecting approximately 2 to 4 percent of adolescents. AIS by definition occurs in children between 10 to 18 years old, in periods of growth spurts and puberty changes. In patients with central precocious puberty (CPP), generally, growth spurts start earlier than their peers. Therefore, AIS in patients with CPP is expected to develop earlier in juvenile age. Especially in girls, both AIS and CPP are more common than boys thus the risk of AIS may be higher in girls with CPP. The purpose of this study was to determine the incidence of idiopathic scoliosis in girls with central precocious puberty and evaluate an influence of gonadotropin-releasing hormone (GnRH) agonists treatment for CPP patients to prevent progression of scoliosis.

Medical records of 655 girls, 338 with central precocious puberty and 317 for control, in three branches of Korea University Medical Centers pediatric endocrinology clinic from March 2014 to September 2018 were retrospectively reviewed. The angle of scoliosis was measured on the standing frontal radiograph of each patients according to the Cobb method and a curve with a Cobb angle of 10 degrees or more is defined scoliosis. For CPP girls, follow up spine radiographs were taken after 1-year of GnRH agonists

treatment, Cobb angles were measured and follow up Cobb angles were compared with initially measured Cobb angles.

An incidence rate of idiopathic scoliosis is 9.3% in total; central precocious puberty girls had a higher incidence (11.5%) than control (6.9%) and statistically significant (p=0.043). LH peak level correlated with Cobb angle and it is statistically significant ($R^2=0.014$, p=0.027). No progression of scoliosis was showed in central precocious puberty girls after 1year of GnRH agonist treatment.

The incidence of idiopathic scoliosis is higher in girls with central precocious puberty. GnRH agonist treatment for CPP may have a preventive effect on AIS. Further longitudinal study regarding the effects of GnRH agonists treatment for patients of scoliosis with central precocious puberty is needed.

P1-269

The impact of Klinefelter Syndrome on quality of life – a multicentre study

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Background: Klinefelter syndrome (KS) is associated with an increased risk of lower socioeconomic status and a higher risk for morbidity and mortality, which may have a significant impact on quality of life (QOL). The objective of this study is to investigate QOL in a large European cohort of men with KS and associate QOL with socioeconomic status, prevalence of somatic disease and mental illness, testosterone supplementation and age of diagnosis.

Material and Methods: Participants were recruited in 14 clinical study centres in 6 European countries which participated in the European DSS life study. 218 men with KS were eligible for inclusion. Male normative data from the European Social Surveys (ESS) was used for comparison.

Clinical data, related to quality of life, social activity and health status were collected.

Results: The WHO physical domain score of men with KS (66.2 ± 19.4 ; n=206) was significantly lower compared to the healthy reference population (76.5 ± 16.2 ; n=1324; p<0.001). The WHO psych domain score of men with KS (n=206) was significantly lower (63.0 ± 17.9) compared to the healthy reference population (67.8 ± 15.6 ; n=1324; p<0.05). The WHO environment domain score of men with KS (69.7 ± 14.9 ; n=206) was comparable to the healthy reference population (70.52 ± 20.7 ; n=1324; p=0.5). The WHO social domain score of men with KS (59.1 ± 22.1 ; n=206) was

significantly lower compared to the healthy reference population (68.2 ± 13.8 ; n=1324; p<0.001). Men with KS reported less engagement in social activities compared to others of the same age (33% vs 49%, p<0.001), and had less intimate friendships (p<0.001). The presence of somatic or mental health problems led to a significantly worse QOL.

Conclusion: Quality of life is significantly impaired in men with Klinefelter Syndrome, most likely due to the presence of somatic and mental health problems. A multidisciplinary approach of healthcare providers might help to provide adequate counselling and treatment to improve quality of life.

P1-270

Large spectrum of DSD phenotype caused by pathogenic variants in Wilms tumor suppressor gene 1

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Introduction: The Wilms tumor suppressor gene 1 (*WT1*) plays an essential role in urogenital and kidney development. Heterozygous germline mutations in *WT1* have been classically associated with Denys–Drash (DDS) and Frasier syndrome (FS). Exonic missense mutations in the zinc-finger region are the cause of DDS and mutations affecting the canonical donor KTS splice site of intron 9 are the cause of FS. New phenotypes, as 46,XX testicular DSD, associated with *WT1* variants have been disclosed with the development of massive parallel sequencing.

Objective: Retrospective analysis of phenotype and genotype correlation of 7 patients with pathogenic *WT1* variants.

Subjects and Methods: Description of 7 patients with heterozygous pathogenic variants in *WT1*. The sequencing was performed by Sanger and by massively parallel sequencing targeted DSD-associated gene panel using Illumina platform.

Results: Six patients, five with 46,XY karyotype and one with 46,XX karyotype, were initially evaluated by atypical genitalia with range chronological age (CA) of 3 to 16 months; and one 46,XY patient with normal female genitalia and primary amenorrhea at age of 16 yrs. Three 46,XY patients underwent bilateral gonadectomy and germ cell tumors (*in situ* gonadoblastoma and unilateral dysgerminoma) were identified in two patients with partial gonadal dysgenesis (PGD) and complete gonadal dysgenesis (CGD) respectively. In both, intronic variants affecting splicing of *WT1* exon 9 were identified, the IVS 9+4C>T and the IVS 9+5G> A variants,

respectively. Two pathogenic missense *WT1* variants: the c.1419 T>A (p.His473Gln) and the c.742 A>T (p.K248X) were identified in two patients with 46,XY PGD, in whom Wilms tumors were diagnosed precociously, at four and six months of life. The novel c.1453_1456del variant in *WT1* was identified in a 46,XX testicular DSD patient. Nephrotic proteinuria was diagnosed in five of six 46,XY patients, 3 of them underwent renal transplantation at 7, 8 and 24 years of age.

Conclusion: Pathogenic allelic variants in *WT1* are associated with a broad spectrum of urogenital abnormalities. In patients with 46, XY gonadal dysgenesis and variants in *WT1* it is mandatory to actively investigate the presence of glomerulopathy. In addition, variants in *WT1* could be the cause of 46,XX testicular.

P1-271

Endocrine and reproductive outcome of men born with various degrees of hypospadias

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Introduction: Limited, small-scale studies have revealed that men with proximal hypospadias (HS) or with other signs of undermasculinisation (i.e. complex HS) are at risk of reduced fertility and/or impaired testicular hormone synthesis. However, the extent of this phenomenon and if milder forms of isolated HS are also affected, remains unclear.

Aims: To explore reproductive hormones and semen quality of young men (16-21 years old) born with all forms of non-syndromic HS in comparison to healthy controls.

Methodology: Cross-sectional assessment was performed at Ghent University Hospital and Wien Medical University (ongoing). Blood sampling was done between 8:00 and 9:00 for total and free testosterone, LH, FSH and Inhibin B measurement. Participants were asked to give two semen samples for a spermogram, according to the WHO 2010 criteria. Statistical analysis was performed using IBM SPSS® 25.0 using an unpaired Student t-test or Mann Whitney-U test as appropriate.

Results: A total of 153 HS (108 distal, 45 proximal) and 42 controls have currently entered the study. No differences in free and total testosterone and DHT levels were found between distal or proximal HS, or between isolated or complex HS, as compared to controls. FSH levels were higher and Inhibin B levels lower in complex HS as compared to isolated HS and controls (FSH: p=0,011 and p=0,005; Inhibin B p=0,001 and p=0,008, respectively). Azospermia was found in 6 (4,3%) HS. Oligozoospermia was present in 24 (17,3%) HS and 1 (2,4%) control. According to the WHO 2010 criteria, 60/139 (43,2%) HS had a normal spermogram as compared to 24/42 (57,1%) controls. In controls, mild asthenozoospermia and teratozoospermia were the most common causes of abnormalities. No difference in semen concentration was found between distal and proximal HS (p=0,557). However, both groups

had lower sperm concentrations as compared to controls (distal: p=0,022; proximal: p=0,040). Men born with complex HS had lower semen concentration as compared to men who had isolated HS and controls (p=0,007 and p<0,001, respectively).

Conclusion: In our cohort, over 20% of men born with HS have reduced semen quality. In contrast to previous studies, no difference in semen concentration was found between proximal and distal HS. However, complex HS was associated with lower semen concentrations. No difference in testosterone or LH levels was found between HS and controls.

P1-272

Age at menarche over the last decades and inter-regional variability in Northern Spain

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Introduction: Menarche is the time of first menstrual bleed and it occurs, on average, 2 to 2.5 years after the onset of puberty. Globally, the age of menarche had been reduced since the last century.

Objective: To examine the evolution of the age of menarche over the last decades and inter-regional variability in an autonomous community located in northern Spain which is divided in eight health areas.

These health areas differ between them from predominance of rural or urban environments.

Material and methods: A retrospective, descriptive studio was made. We revised the age of menarche of girls and teenagers born between 1920 and 2008, in the eight health areas. These data were collected from clinical records and electronic medical history from ninety public primary health centers of all health areas of the region.

We did two analysis. First, birth decade was compared with age at menarche. Second in the teenagers born between 1998 and 2008, the age of menarche was compared with the health area to which they belonged.

Results: The second analysis showed differences in the mean age at menarche by health area, ranged between 11.78 (0.87) years in the most rural area to 11.55 (0.92) years in the most industrialized area (p<0,05).

Conclusions:

- The average menarcheal age decreased through the last decades. It is probably due to both genetic and environmental factors.
- The differences found in the mean age of menarche by belonging health area were statistically significant but maybe they aren't clinically significant. In order to know the influence of environmental factors over the onset of the menarche, a more detailed study should be performed.

Table 1: Birth decade vs age at menarche

Birth decade	Mean	Median	Age at menarche (years)		
			Mode	DS	N
1920-1929	14.29	14	14	1.92	91
1930-1939	13.94	14	14	1.96	540
1940-1949	13.18	13	14	1.7	3594
1950-1959	12.77	13	13	1.54	6183
1960-1969	12.75	13	13	1.54	4791
1970-1979	12.78	13	13	1.5	13196
1980-1989	12.62	13	12	1.54	16590
1990-1999	11.84	12	12	1.06	13126
2000-2010	11.64	12	12	0.9	10375

P1-273

Hypergonadotropic hypogonadism in 46, XX adolescents without gonadotoxic therapy: Clinical features and molecular etiologies

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Background: Hypergonadotropic hypogonadism(HH) in females results from primary gonadal failure related to genetic defects affecting ovarian development and function or acquired gonadal damage; limited knowledge exist regarding underlying genes involved or potential gene X environment interactions responsible for disease trait manifestations. While pathogenic variants in single genes, chromosomal abnormalities such as Turner syndrome and acquired gonadal damage have been described as etiologies of HH, over 75% of cases do not have a clear molecular diagnosis.

Methods: Twenty-eight females with 46,XX HH from a single pediatric endocrinology center were studied. Patients with gonosomal chromosomal abnormalities and gonadal failure secondary to chemotherapy/surgery were excluded. Ascertainment was based on characteristic clinical and laboratory features. Potential molecular genetic etiologies were investigated by family based genomics as a means to gain insights into disease biology.

Results: Mean age at diagnosis was 15.1 ± 2.3 years; clinical presentations included primary amenorrhea(PA) in 19(67.9%), secondary amenorrhea(SA) in 5(17.9%), short stature in 3(10.7%) and breast underdevelopment with irregular menstrual cycles in 1(3.5%). Consanguinity ratio was 71.4% and 25% of the patients had a family member with HH. Height and BMI SDs were -0.8 ± 1.1 and 0.6 ± 1.5 , respectively. There was no breast development in 25% of patients, while 43% of them at breast Tanner stage IV-V (BIV-V). Mean LH and FSH levels were 27.1 ± 9.7 mIU/ml(Ref:2.4-12.6) and 82.2 ± 30.8 mIU/mL(Ref:3.8-8.8), respectively. There were no differences in FSH, LH levels, height or BMD SDs between the PA and SA groups, but length of the uterine long axis differed (34.6 ± 11.8 vs. 54.6 ± 13.0 mm, p:0.004). Lumbar spine BMD Z-score with DXA was -1.8 ± 1.1 , 41.9% of them had Z-score <-2. Final height and MPH SDs were -0.2 ± 1.0 and -0.5 ± 0.9 , respectively.

Median time from initiation of estrogen to combined hormone replacement therapy was 18.1 and 1.1 months in PA and SA groups, respectively (p=0.012). Likely damaging pathogenic variants were identified in 14 patients (50%); genes included SOHLH1 (n:2), NO-BOX, PAD16, MRPS22, GALT (n:2), CYP17A1, MSH5, MCM9, MCM8 and C3. Multi-locus pathogenic variation was detected in 2 cases. Patients with galactosemia (GALT) presented with PA, and their urinary reducing substance levels were normal.

Conclusion: At least 50% of HH cases have a molecular diagnosis in a gene that contributes to gonadal development and maintenance, that participates in estrogen biosynthesis, or that has been implicated in diminished ovarian reserve. Additionally, standard laboratory screening can fail to identify galactosemia.

P1-274

Quality of life in Chilean transgender children, adolescents, and their parents

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Background: Quality of life (QOL) includes physical, psychological and social aspects. Transgender (TG) children undergo problems in school and with family, friends, and social relationships. These adverse effects on physical and psychosocial health can impair their quality of life.

Objective and Methods: This study aims to assess health-related quality of life (HRQOL), using the KIDSCREEN-52 questionnaire (Spanish version, administered via e-mail) in a group of Chilean transgender children (8–18 years) and their parents, and compare them with Chilean cisgender (CIS) children. All scores were standardised according to the KIDSCREEN manual. Higher scores indicate greater HRQoL.

Results: Thirty-eight children completed the questionnaire, aged 8.4–18 years. 21 were TG: 6 (29%) transfemale (14.3 [10.9–15.7] years) and 15 (71%) transmale (15.2 [14.0–18.0] years). 17 were cis- children: 13 females (76%) (10.6 [8.7–13.1] years) and 4 males (24%) (13.6 [10.5–14.4] years). Sixty-two parents' questionnaires were completed: 33 from transgender families: 45% transfemale and 55% transmale, and 29 questionnaires from cisgender families: 72% females and 28% males. Results are shown in Table 1.

HRQOL scores were lower in TG children compared to CIS children in all domains. The worst domains in TG children were "Moods & Emotions", "Psychological Well-being" and "Social Acceptance". The better domain was "School Environment"

Table 1: KIDSCREEN results

	TRANS Subjects (n= 21)		CIS Subjects (n=17)		p	TRANS Parents (n=33)		CIS Parents (n=29)		p
	mean	SD	mean	SD		mean	SD	mean	SD	
Physical Well-being	43.04	15.2	59.59	8.84	***	48.26	13.58	62.66	6.65	**
Psychological Well-being	38.36	16.7	56.91	5.63	***	49.18	11.97	59.32	7.57	**
Moods & Emotions	31.11	17.6	55.05	7.97	***	38.97	15.38	52.45	8.34	**
Self-Perception	41.72	11.3	56.29	5.91	***	40.18	7.63	50.35	4.62	**
Autonomy	45.29	11.8	56.06	6.76	**	49.26	8.98	55.42	6.33	NS
Parent Relations & Home Life	46.03	8.72	56.34	4.62	***	52.52	7.04	54.94	5.91	*
Financial Resources	44.94	11.4	52.32	6.57	**	49.90	9.41	55.32	7.47	NS
Social Support & Peers	46.47	13.6	56.61	7.31	*	51.61	10.11	55.14	8.8	**
School Environment	50.05	11.1	59.78	5.67	**	53.57	8.93	60.47	5.3	**
Social Acceptance	38.77	13.1	50.21	8.77	**	40.73	11.51	49.70	7.65	**

***p<0.001, **p<0.01, *p<0.05

Conclusion: Our results revealed that TG children have worse QOL compared to CIS children. The worst results were related to mental health issues. Obtaining this information it is important to identify these problems in order to improve their quality of life.

P1-275**Long-term outcome of testicular function in nonclassic lipoid congenital adrenal hyperplasia**

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Background: Lipoid congenital adrenal hyperplasia (LCAH) is caused by mutations in STAR and characterized by defect in adrenal and gonadal steroidogenesis and lipid droplet accumulation in steroidogenic cells. 46,XY patients with classic LCAH typically present with female-type external genitalia, while those with nonclassic LCAH have masculinized external genitalia. The rarity of the nonclassic form precludes the clarification of pubertal and reproductive functions in this condition.

Objective: The aim of this study was to define long-term outcome of testicular function in nonclassic LCAH.

Methods: We retrospectively reviewed medical charts of three Japanese males with nonclassic LCAH in our institution. We also performed genetic analysis of STAR and functional assay of a novel sequence variation of STAR.

Results: Our patients were diagnosed with primary adrenal insufficiency (PAI) at 5 days, 4 years, or 5 years of age. All exhibited complete male external genitalia and completed pubertal development without androgen replacement. Endocrinological data showed preserved testosterone synthesis, despite increased gonadotropin levels in Patients 2 and 3. Semen analyses showed normozoospermia in Patient 1 and mild oligozoospermia in Patient 2. Electron microscopic analysis of testicular biopsy from Patient 2 at 13 years of age revealed prominent lipid accumulation in the cytosol of Leydig cells. Sanger sequencing identified the same compound heterozygous mutations in STAR (p.Glu258* and p.Arg272Cys) in Patients 1 and 2 and a heterozygous dominant-negative mutation in STAR (p.Gly22_Leu59del) in Patient 3. Functional assay of STAR-Arg272Cys with COS-1 cells determined the residual activity as 35% of the wild-type STAR.

Conclusion: These results indicate that testosterone synthesis in nonclassic LCAH can be preserved to complete pubertal development and to induce germ cell maturation despite lipid accumulation of the Leydig cells.

P1-276**A Cross sectional study of serum gonadotropins, testosterone and genital parameters during mini puberty in normal male infants**

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Introduction: The onset of puberty is preceded by the activity of the hypothalamic-pituitary-gonadal (HPG) axis during infancy known as mini-puberty which is sexually dimorphic and more pronounced in male infants.

Aims and objectives: The main objective was “To study LH(*Luteinising hormone*), FSH(*follicle stimulating hormone*) and Testosterone and testicular volume, stretched penile length (SPL) during mini-puberty in males”

Material and methods: A multipoint single contact cross-sectional study which included 133 consecutive healthy full-term male, taken on day 3 of life (n=46), at 2-6 weeks (n=32), 7-12 weeks(n=32), 13-16 weeks (n=18) and five infants > 6 months age. LH, FSH, testosterone were measured by Immulite 1000 CLIA(*Chemiluminescent immunometric assay*) testicular length, breadth was measured using Vernier Callipers and testicular volume by the formula of ellipsoid(length×width²×pi/6) and SPL(stretched penile length) using *Schonfeld's* method.

Results: (*table*) LH and FSH levels were highest in 2-6 weeks age group and thereafter gradually decreasing values of LH and FSH were observed till 6-12 months age.

Highest Testosterone levels were observed on day 3 of life but not accompanied with rising LH, FSH, possible explanation may be higher levels of the HCG due to decreased metabolic clearance of HCG or high level of SHBG.

SPL mean(SD) at birth was 3.06 ± 0.039 cm and $3.85(0.06)$ cm at 2-6 week, $4.10(0.04)$ cm at 7-12 week, $4.23(0.05)$ cm at 13-16 week, and $4.34(0.07)$ cm at >6 months there was a significant change with the increasing age group.

A change in testicular volume was observed mean(SD) from $0.30(0.16)$ ml at birth to $0.43(0.12)$ ml at 2-6 week, $0.56(0.12)$ ml at 7-12 week, $0.69(0.18)$ ml at 13-16 week, and $0.92(0.15)$ ml at 6 months. There is a gradual increase in the SPL and testicular volume in mini-puberty.

Conclusion: Postnatal gonadal surge is associated with significant change in testicular and genital growth.

Table 1: Table showing median, range and lower & upper quartiles for the LH, FSH, testosterone in different age.

Age Group	Testosterone(ng/dl) Median(range)LQ-UQ	LH(mIU/ml)	FSH(mIU/ml)
Day 3 N=46	144 (40-330) 91.6-229	0.334(0.1-0.85) 0.1-0.56	0.352(0.12-0.98) 0.2-0.53
2-6 weeks N=32	102.8(38-390) 75.4-170	3.465(1.09-20.9) 2.3-5.63	2.02(0.55-6.66) 1.25-3.59
7-12 weeks N=32	89.95(36-273) 57.5-131	2.385(0.95-6.38) 1.54-3.81	1.64(0.62-39.8) 1.19-2.13
13-16 weeks N=28	77.45(22-179) 43.7-113	1.96(0.81-4.63) 1.43-3.21	1.89(0.96-2.96) 1.43-2.33
>6 month, N=5	<20	0.315(0.18-0.63) 0.21-0.48	1.02(0.43-1.32) 0.56-1.25

A novel MAP3K1 gene mutation (c.556A>G) associated with 46, XY complete gonadal dysgenesis

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Introduction: Complex and ordered intracellular signal pathways play a significant role in sex determination in mammals, mediating the balance of gonadal development. A major pathway involved in the regulation of the male development is mitogen-activated protein kinase (MAPK) signaling pathway. To date, mutations of *MAP3K1* gene have been found to account for approximately 15%-20% of 46, XY gonadal dysgenesis (46, XY GD).

Objective: To determine and clarify the presence and functional consequence of the deleterious mutation in *MAP3K1* gene of the patient with 46, XY complete gonadal dysgenesis (46, XY CGD).

Case presentation: Our patient, a 13-year-old girl, was first seen at our hospital because of undeveloped breasts and primary amenorrhea. On physical examination, her breasts development was B2 stage and pubic hair was PH1 stage without axillary hair. She had female external genitalia and small uterus. Endocrinological investigations revealed hypergonadotropic hypogonadism (FSH 107.10 IU/L, LH 32.89 IU/L, E2 11 ng/L, PRG 0.46 ug/L), and Cytogenetic studies showed a 46, XY karyotype. Owing to the possibility of gonad's deterioration, the patient underwent bilateral gonadectomy. Moreover, the older sister of the patient had a similar symptom but the detailed information was unknown.

Methods and Materials: Whole-exome sequencing was performed in the patient and her family members. The *MAP3K1* gene was PCR amplified and directly sequenced. The functional study was also performed to find out the interaction between the testis-development pathway and ovary-development pathway.

Results: We identified a heterozygous *MAP3K1* gene mutation (c.556A>G, p.R249G) in the patient and her mother, which located in exon 2. Predicted results of prediction sites (Polyphen-2 and Mutation Taster) showed that the mutation was pathogenic. In vitro study showed a significantly increased phosphorylation of p38 and ERK1/2 and an obviously reduced expression of SRY gene, compared to the wild-type cells. Causing by the gain-of-function mutation, the stabilization of beta-catenin and degradation of SRY hinder the formation of the testis.

Conclusions: In our study, we describe one patient diagnosed with 46, XY CGD, carrying a novel mutation of *MAP3K1* (c.556A>G). The results emphasize the role of *MAP3K1* in human sex development and demonstrate MAPK pathway can tilt the balance of sex determination by regulating the expression of sex-related gene.

Gender mender, or defender: Understanding decision making in Aotearoa/New Zealand for people born with a variation in sex characteristics

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People born with a variation in sex characteristics (VSC) face the challenge of having atypically sexed bodies. This quantitative study recruited 10 young adults with a VSC (14 to 24 years); 18 parents of children with a VSC; and 22 health professionals working in the VSC field. Interviews were semi structured, digitally recorded and transcribed. Using thematic analysis, we identified key themes regarding participants' experiences of health care decision-making. This study has been conducted in collaboration with the Intersex Trust of Aotearoa/New Zealand (ITANZ).

This research is original and innovative in three ways – it demonstrates close collaboration between activists and academics through all stages of the research design and conduct; it provides a unique 360-degree perspective integrating the views of health professionals, parents and young people (possible because of the small size of New Zealand); and it fills a gap in the literature by capturing the voice of current young people living with a VSC.

Health professionals, parents and young people must navigate complex and controversial healthcare decision making – often ethically challenging, involving multiple decision points throughout their life, with divergent and uncertain consequences. This study documents key elements that influence healthcare decision making as reflected in the data. These include; understanding of diversity, communication skill, bias, conforming to or disrupting norms, psychological/peer support, bodily autonomy, identity, expectations, future worries, what's right and recognition of the past. "Trust" was a meta-theme that underpinned all of these elements.

The implications of these findings include targeted education and training for health professionals to: increase their awareness and insight regarding bias, diversity; advance communication skills; understanding patient perspectives; and addressing ethical issues. Provide specialised psychological support and peer support for parents; increase their awareness and insight regarding bias, diversity and address future concerns with a focus on bodily autonomy for the child. Young people need caring communities established through peer and specialised psychological support to explore their sense of identity, understanding of diversity and acceptance of self. Health system improvements include: Multi-disciplinary teams including psychologists and patient advocates; Specialist national centre in Aotearoa/NZ and DSD patient registry and ongoing research looking at outcomes.

P1-280**Glucose tolerance and beta cell function in adolescents with polycystic ovary syndrome from North India**

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Introduction: Glucose tolerance and beta cell function can be abnormal in polycystic ovary syndrome (PCOS) patients because of obesity and/or PCOS per se.

Methods: Various indices derived from 2 hours oral glucose tolerance test (OGTT) were compared in 46 adolescents with PCOS (mean age 17.6 ± 1.9 years and mean body mass index (BMI) $24.5 \pm 5.4 \text{ kg/m}^2$) with age comparable controls (n=25, mean age 19.2 ± 2.3 and BMI $21.7 \pm 2.8 \text{ Kg/m}^2$)

Results: PCOS girls had significantly higher waist circumference (WC) (80.4 ± 11.6 vs 72.1 ± 7.0 ; p=0.006), mean systolic blood pressure (SBP) (116.6 ± 11.1 vs 107.7 ± 7.8 ; p=0.001) and LDL cholesterol (115.7 ± 37.2 vs 90.3 ± 21.4 ; p=0.008) as compared to controls. Fifty percent of PCOS girls had WC >80 cms and about 60% were overweight or obese (BMI>80th centile for Indian standard). The prevalence of impaired glucose tolerance according to ADA criteria (4/46 in PCOS versus 2/25 in controls) and metabolic syndrome according to ATP III criteria (3/45 vs 0/25) was similar in PCOS girls and controls. The area under curve (AUC) for glucose was similar in both groups (median, range 135, 66-189). AUC for insulin (median, range, 696, 452-1790 versus 126, 670-1383; p=0.01), fasting c-peptide in nmol/L (median, range 4.4, 0.4 to 182.6 versus 0.6, 0.4 to 1.3, p=0.002) and delta c peptide at 30 minutes from baseline (10.5, 1.6-15.6 versus 1.7, 0.5-5.1; p=0.006) was significantly higher in PCOS as compared to controls. The fasting c-peptide correlated significantly with the delta c-peptide at 30 minutes ($r^2=.79$, p=0.01) There was no difference in the anthropometric measurements, metabolic parameters and the AUC for glucose and insulin derived from OGTT between obese or lean and normal weight PCOS adolescents. Disposition index an estimate of beta cell response to prevailing insulin sensitivity was similar in obese and lean and normal weight PCOS girls.

Conclusions: In this cohort of adolescents with PCOS from North India glucose tolerance was maintained with higher insulin secretion as evidenced with higher AUC for insulin, higher fasting c-peptide and higher delta of c peptide at 30 minutes signifying underlying beta cell dysfunction. Metabolic abnormalities and beta cell dysfunction seen in this cohort of PCOS is likely due to the PCOS status than obesity.

P1-281**Virilization of a girl at puberty due to a unique translocation of an abnormal duplicated Y-chromosome to a deleted chromosome 9 including the DMRT1 gene**

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Background: Virilization at puberty in girls remains a challenge. Several differential diagnoses must be considered including disorders of sex development (DSD) and tumors.

Case Report: We report an 11.5-year-old girl who was referred to our center for progressive cliteromegaly since 6 months. Past medical history was remarkable for prematurity of 36 weeks gestation and for mild ongoing psychomotor delay. At presentation physical exam revealed normal height (P10) with slight disproportions and an overweight with BMI P90. She showed otherwise a normal systems exam and no syndromic features. Pubertal stage was P5, B1-2, A1-2 with rich bodily hair. External genitalia revealed a marked cliteromegaly of 3.5x1.5cm in size, but was otherwise normal looking female. No gonads were palpable. First line investigations revealed normal adrenals and gonads with a prepubertal uterus by ultrasound; no tumor was found. Bone age was normal. Laboratory studies showed a significant androgen excess. LH and FSH were both elevated (FSH>>LH) and E2 undetectable. Second line investigations showed normal adrenals and gonads by MRI. AMH was very low. 24h urine steroid profiling excluded any form of late-onset CAH but confirmed very high excretion of androgen metabolites. ACTH stimulation test showed normal reactivity of adrenals steroids, while dexamethasone test suppressed normally. Karyotype was 45,X.

Objective: 1)How to explain androgen excess in a 45,X girl at puberty? Where is the Y-material hidden? 2) What to do with a suspected androgen secreting gonad in 45,X at puberty?

Methods: Expanded genetic exams in search of a hidden Y-chromosome including cytogenetic SRY-FISH analysis and genomic Array-CGH. Exploration of the gonads by laparotomy and histopathological investigations.

Results: Genetic analysis (Karyotype, FISH and Array-CGH) showed 45,X.ish der(9)t(Y;9)(SRY+) plus a terminal heterozygote deletion 9p24.3-p23 resulting in a partial monosomy 9p including 49 genes, e.g. the sex gene *DMRT1* explaining a complete sex reversal phenotype. Given these results, the patient underwent laparoscopic gonadectomy. A dysgenetic gonad was found on the left with normal looking Leydig cells and granular Sertoli cells, but no germ cells. A streak gonad was detected on the right. No signs of malignancy were found.

Conclusions: Virilization at puberty may be more complex than routinely thought. All efforts should be taken to find the underlying cause as ongoing virilization may result in irreversible

bodily changes. Repeat and expanded biochemical and genetic workup may be necessary to solve complex cases. Multiple genetic hits can manifest with unique, unsuspected phenotypes.

P1-282**Characteristics of 311 children with early onset pubertal signs. Descriptive study**

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Aim of our study was to assess clinical characteristics and complementary studies, in patients who consulted the Endocrinology Department of our pediatric hospital, referred by pediatricians to discard precocious puberty.

Methodology: it is a descriptive study based on review of medical records, with first consultation between 2010 and 2018. Criteria were developed to assign patients to one of six diagnostic categories based on age, growth, and clinical findings, biochemical and imaging studies (bone age, pelvic ultrasound and MRI). We classified our 311 patients in 6 diagnostic groups: involute precocious breast development, early non-progressive breast development, central precocious puberty (PPC), peripheral precocious puberty (PPP), advanced puberty and rapidly progressive puberty. Exclusion criteria: not going to follow-up visits. Statistical analysis by SPSS 23.

Results: we examined a total of 311 medical records (14 men, 297 women), referred by their pediatricians by early onset pubertal signs, attended the first visit to the endocrinology department with an average age of 7.8 years (95%CI:7.7-8). The distribution of subjects was: involuted precocious breast development (n=25), non-progressive precocious breast development (n=19), PPC (n=156), PPP (n=3), advanced puberty (n=88) and rapidly progressive puberty (n=20). Male subjects who were diagnosed of precocious puberty had at first visit a mean age of 8.7 years (95%CI:7.8-9.5), and women had a mean age of 7.7 years (95%CI:7.5-8). There was a significant difference regarding bone age at diagnosis (more advanced in central precocious puberty and rapidly progressive puberty). There was a statistically significant association between precocious puberty and the fact of being adopted (X^2 : 11.262; p: 0.046). The LH at 3 hours of the GnRH test was significantly higher in the PPC group (mean value of LH 14UI/L, IC95%:11.5-16.6) compared to the others. Patients with PPC were identified who did not meet the classic criteria of the diagnosis of PPC in the Procrin test, however they presented clinical characteristics in the follow-up that led to the diagnosis. We found relation between having MRI findings and presenting PPC (X^2 : 38.262; p: 0.000), however incidental findings where found in MRI of patients with advanced puberty. A total of 69% of patients with PPC and 17.6% patients with advanced puberty (including here the rapidly progressive forms) received treatment.

Conclusions: we present dates of a population of children of both sexes with clinical manifestations suggestive of precocious/advanced puberty evaluated and followed between the years 2010 and 2018. The results coincide with those described in previous studies.

Thyroid

P1-283**Children with Hashimoto's thyroiditis have increased intestinal permeability: Results of a pilot study**

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Background: Both genetic and environmental factors serve as the trigger of Hashimoto's thyroiditis (HT), but the exact mechanisms are still not fully understood. Increased intestinal permeability was shown to be a constant and early feature of several autoimmune disorders. Although HT is the most common autoimmune disorder worldwide, the role of intestinal permeability in its pathogenesis had received little attention. Human zonulin modulates intracellular tight junctions and controls intestinal permeability. Zonulin level in blood is considered as a useful marker of intestinal permeability.

Objective: To examine the hypothesis that patients with HT have increased intestinal permeability.

Methods: This was a case-control study on a group of 30 children and adolescents with HT, and age, gender and body mass index (BMI) matched 30 patients with congenital hypothyroidism (CH). Serum zonulin levels, free thyroxine (fT4), thyroid stimulating hormone (TSH), anti-thyroglobulin antibody and anti-thyroid peroxidase antibody were measured.

Results: Zonulin levels were significantly higher in patients with HT than patients with CH (59.1 ± 22.9 vs. 43.3 ± 32.9 , p=0.035). Age, gender, weight SDS, height SDS, BMI SDS and levothyroxine dose were not different between the groups. In patients with HT, zonulin levels were positively correlated with weight ($r=0.406$, p=0.03), BMI ($r=0.486$, p=0.006) and levothyroxine dose ($r=0.463$, p=0.02). In patients with CH, zonulin levels were positively correlated with age ($r=0.475$, p=0.008), weight ($r=0.707$, p<0.001), BMI ($r=0.872$, p<0.001) and levothyroxine dose ($r=0.485$, p=0.007). After adjusting for age, weight, TSH and fT4 levels, zonulin level was only associated with levothyroxine dose in patients with HT ($R^2=0.36$, p=0.05). When we put the patients with CH in the same regression model, only weight was associated with zonulin level ($R^2=0.62$, p<0.001).

Conclusion: Results of this first study examining zonulin levels in patients with HT suggested increased intestinal permeability in these patients. In addition, the association between zonulin levels and levothyroxine dose might imply a relationship between serum zonulin and disease severity.

P1-284**Different Endocrine Affects in DICER-1 Syndrome**

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Introduction: DICER1 syndrome is a pleiotropic, autosomal dominant familial genetic tumor predisposition syndrome. DICER1 somatic + germ-line mutations (double hit hypothesis); cystic nephroma; pleuropulmonerblastoma, ovarian sex cord-stromal tumors, multinodular goitre (MNG) are associated with many conditions such as differentiated thyroid cancer, pituitary blastoma. We presented three cases, two of whom were siblings, who had been consulted because of non-menstruation and goitre and had the same diagnosis despite their different characteristics.

Case 1: A 15-year-old girl presented with menstrual irregularity, hairing increase and neck swelling. In physical and laboratory examination; goitre, muscular appearance in the arms-legs, hirsutism, fat loss in the cheeks, increased fat tissue in the gluteal region, hyperandrogenism, insulin resistance, low leptin, MNG, total body MRI revealed signs of partial lipodystrophy Metformin was started. Nodul cytology; follicular neoplasia was suspected due to near totale thyroidectomy. In the follow-up new nodule development in residual tissue and growth in existing nodules are observed. In the first year of follow-up, an increase in hyperandrogenism and an increase in tumor markers and an ovarian mass occurred despite of metformin treatment. After protective ovarian surgery; Sertoli-Leydig cell tumor was diagnosed. Somatic mutation was detected in DICER1 gene. Germ-line mutation examination is still ongoing.

Case 2-3: She was referred to the goiter at the age of seven years and she was operated for multicystic nephroma-neuroblastoma at the age of 14 months. Follicular neoplasia was detected in MNG-nodul cytology. Total thyroidectomy was performed. Somatic + germ-line mutation was detected in DICER1 gene. When the sister of the case was evaluated at the age of six, MNG was detected and in the follow-up; nodules growth, development of new nodules while first cytology was benign; total thyroidectomy was performed due to the detection of unclear atypia in final sampling. Papillary carcinoma suspicion and a germline mutation were detected in DICER1 gene. A somatic mutation examination was planned.

Conclusion: Although DICER1 syndrome is a tumor predisposition syndrome, it can also perform endocrine effects (MNG, differentiated thyroid cancer, ovarian sex cord-stromal tumors, pitutier blastoma-related diabetes insipitus / Cushing's disease. Here previously not reported rare cases with acquired partial lipodystrophy are presented which had similar features of MNG.

P1-285**Evaluation of Thyroid Function Tests in Children with Chronic Liver Diseases**

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Backgrounds /Aims: Studies related to changes in thyroid hormone metabolism in the course of chronic liver diseases have been conducted mostly in adults. In this study, we aimed to investigate the thyroid dysfunction in childhood chronic liver diseases.

Methods: Between 2005 and 2018, 960 chronic liver disease patient file that followed in our gastroenterology department are reviewed. Among all study subjects, 107 (53 female, 54 male) patients aged between 1 month and 18 age who were diagnosed as chronic liver disease and had thyroid function tests during diagnosis in their file, were enrolled in the study group. Anthropometric characteristics, laboratory data (ALT, AST, ALP GGT, total bilirubin, direct bilirubin, indirect bilirubin, albumin, total protein), and thyroid function test values were obtained from patient files.

Results: Of the 107 patients, 93 (86.9%) had normal thyroid function test and 10 (9.4%) had subclinical hypothyroidism and four (3.7%) had euthyroid sick syndrome. Of the 10 patients with subclinical hypothyroidism, two had glycogen storage disease, three (30%) had biliary atresia, one had undiagnosed cholestatic liver disease, one had Alagille syndrome, one had chronic viral hepatitis, one had inborn errors of metabolism (galactosemia) and one had persistent elevated liver enzymes (idiopathic hepatitis). Spearman correlation analysis showed a negative correlation between free T3 and direct bilirubin ($r = -0.329$, $p = 0.027$).

Conclusion: In conclusion, euthyroid sick syndrome or sub-clinical hypothyroidism can be seen frequently in children with chronic liver diseases. Therefore, thyroid function tests should be evaluated in these cases at the diagnosis and monitoring. Moreover, this study is the first to show a negative correlation between free T3 levels and direct bilirubin, suggesting the association between the disease severity and the thyroid function test.

Key Words: Childhood chronic liver diseases, thyroid function test, euthyroid sick syndrome, subclinical hypothyroidism.

Identification of a THRA mutation in a 2yr old child with clinical features of hypothyroidism and multisystem involvement

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Background: Thyroid hormones act via receptors (TR α ; TR β) encoded by separate genes (*THRA*, *THRB*). Mutations in *THRA* are a recently-recognised cause of Resistance to Thyroid Hormone alpha (RTH α), a disorder with tissue-specific hypothyroidism but near-normal thyroid function tests.

Aim: We describe the youngest recorded case of RTH α , in a 2yr old boy with disproportionate short stature, global developmental delay, constipation and a heterozygous missense mutation (p.G291S) in *THRA*.

Case Report: A 16-month old male was referred to endocrine clinic with short stature. He had disproportionate stature with reduced subischial leg length (Table 1). He is in care, with a maternal antenatal history of substance abuse (exposure to methadone, heroine and alcohol in utero). He has global developmental delay and is mildly dysmorphic with constipation, all attributed to chromosome 16p13.11 microduplication.

Examination revealed coarse facial appearance, depressed nasal bridge, long philtrum and central hypotonia. He had delayed visual maturation, hypermetropia, small kidneys and gastroesophageal reflux. His motor milestones (unable to sit without support) and speech are delayed. Laboratory analysis revealed normocytic anaemia, elevated creatine kinase levels, low-normal T4 and elevated T3 levels leading to altered T4:T3 ratio, with normal TSH levels. *THRA* sequencing identified a heterozygous missense (p.G291S) mutation, which is homologous to a known pathogenic mutation in *THRB* (G345S), causing RTH β . Correlation of genotype with phenotype and assessment of response to thyroxine therapy (25mcg/day) is being undertaken.

Conclusion: We suggest that *THRA* sequencing should be considered in patients with clinical features of hypothyroidism, raised CK, anaemia and near-normal thyroid function tests but altered T4:T3 ratio. This case broadens the phenotypic spectrum of RTH α .

Table 1: Clinical and biochemical characteristics

Variables	2019
Age	2.34y
Weight (Kg)	13.35 (-0.21SDS)
Height (cm)	81.0 (-1.9 SDS)
Sitting Height (cm)	46.5 (-3.27 SDS)
Subischial leg length (cm)	34.5
BMI (kg/m ²)	20.35 (2.79 SDS)
Thyroxine dose	None
TSH (mU/L) (rr 0.7-6.0)	2.63
Free T4 (rr 12- 22 pmol/L)	10.8
Free T3 (rr 3.5-8.5 pmol/L)	10.7
TPO (<15 iu/L)	Negative
CK (μL) (rr 40-320 U/l)	388
RBC mass (Oct 2018) (4.6– 6.2x 10 ¹² /L)	3.68
IGF1 nmol/L (2-20nmol/L)	6.8
Peak Cortisol (nmol/L) from Short synacthen test (rr >550nmol/L)	740

The comparison of natural course thyroid autoimmunity in children and adults with type 1 diabetes: from the diabetes onset up to five years of its duration

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Introduction: Individuals with type 1 diabetes (T1D) are at higher risk of developing other autoimmune disease, including autoimmune thyroid diseases (AITD). The incidence of Hashimoto among people with T1D varies between 8 and 50%, depending on gender, age and ethnicity.

Aim: To evaluate prevalence of anti-thyroid peroxidase (anti-TPO) and its correlation to the presence of thyroid dysfunction in children and adults at diagnosis of T1D and in the five-year observation.

Methods: The study included 367 patients (218 children; 149 adults) at T1D onset. Anti-TPO level and thyroid function tests (T4, T3, and TSH) were performed within 5 days of the initial diagnosis of diabetes and during the five-year follow-up period.

Results: At T1D onset, anti-TPO was reported in 18.5% of patients, more frequently in adults than in children (26.2% vs. 13.3%, p=0.001). In children, anti-TPO was observed mostly in girls (62.1% vs. 37.9%, p=0.047), while there was no gender association in adults (females 56.4% vs. men 34.6%; p=0.754). Positive anti-TPO patients had higher occurrence of GADA (83.8% vs. 70%, p= 0.03) and higher level of its titer [median 38.7 (IQR:5.4-512.4) vs. 6.2 (1.1-40.6), p<0.0001]. Whereas, in children higher titer of IAA was observed [6.5 (5.3-8.2) vs. 5.6 (5.0-6.9), (p=0.026)].

Hypothyroidism (HT) at diagnosis of T1D occurred more frequently in adults than in children (9 vs. 2, p=0.009), in 3 positive anti-TPO adults autoimmune hyperthyroidism was noted (elevated titers of anti-TSH-R). Positive anti-TPO adults had higher TSH concentration as opposed to negative anti-TPO group (3.6 ± 0.9 vs 1.7 ± 0.9 , p=0.026), such a relationship was not observed among children. HT was diagnosed in 41.4% anti-TPO positive children at T1D onset in the five-year follow-up period, significantly more often in girls than in boys (83.3% vs. 16.7%). While, only next 15% of adults with initially positive anti-TPO developed HT during the study period. The mean time from T1D diagnosis to HT development was 2.8 ± 1.7 years.

Conclusions: Anti-TPO tended to occur more frequently in adults with newly diagnosed T1D without gender association, whereas in children anti-TPO was observed significantly more often in females. The presence of a positive anti-TPO titer was related to a higher incidence of HT at T1D onset in adults. While, in children, the occurrence of a positive anti-TPO titer at T1D diagnosis was associated with a greater risk of developing HT in 5-year follow-up period. The results of the study confirm the validity of screening for AITD at the time of T1D diagnosis and further thyroid function assessment should be recommended.

P1-288

Outcomes of persistent hyperthyrotropinaemia in well term infants

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Background: Neonatal hyperthyrotropinaemia (HT) is defined by elevated thyroid stimulating hormone (TSH) and normal free-thyroxine (FT4) level. Persistent HT in the neonatal period is often a diagnostic dilemma for clinicians to either treat to prevent subclinical hypothyroidism or to wait and monitor thyroid function tests (TFTs).

Methods: As part of an audit, 1,449 term infants who had TFTs undertaken as part of a prolonged jaundice screen from 2012-2017

were reviewed. Infants with HT (defined by TSH>5mU/L) were followed up in clinic. We evaluated perinatal factors and TFTs were monitored in 2-4 weeks, then regularly 2-4 monthly until 2 years of age or until HT resolved.

Results: There were 37 term infants (27 males) with a raised TSH (>5mU/L) and normal FT4 level over the 5-year period. This represents 2.6% of the 1,449 term infants found to have HT. All infants with HT were born in good condition. Mean gestation was 38.1 weeks (± 2.1 SD, range 33.1-42.0). 4 infants had Trisomy 21 and 3 infants had a maternal history of hypothyroidism. In 2 infants, we started levothyroxine treatment due to rising TSH and falling FT4 levels. 9% of infants had TSH normalised to 5mU/L in 4 weeks without treatment, 54% normalised their TSH in 8 weeks, 83% normalised in 3-6 months, 94% normalised in 12 months and 1 patient had persistent TSH >5mU/L which did not require treatment at 24 months.

Conclusions: In 95% of all the cases of HT in well term infants, the natural course was that the TSH resolved to normal < 5mU/L by 2 years of age. In 3% of cases, TSH remained elevated (> 5mU/L) at 2 years but FT4 levels were normal and in the upper quartile range (>15pmol/L) without treatment. We recommend TFTs monitoring due to the risk of decompensation although the risk of decompensation is low; and frequency of monitoring can be reduced after 2 years.

P1-289

Thyroid peroxidase antibodies in children with HLA-conferred susceptibility to type 1 diabetes

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Introduction: The prevalence of thyroid peroxidase antibody (anti-TPO) positivity is estimated to be around 3-4% in healthy children and is remarkably higher in children with type 1 diabetes (T1D). However, anti-TPO positivity in children with HLA-conferred susceptibility to T1D who are not yet diagnosed with T1D, is not well studied. The aim of this study was to describe the prevalence of positive anti-TPO and its effect of thyroid function in children with a genetic susceptibility to T1D.

Methods and subjects: Two hundred twenty-five children (114 boys) aged 7.5 to 10.4 years from the Estonian DIABIMMUNE birth cohort were studied. None of them had a known thyroid disease, two children were previously diagnosed with T1D and two were diagnosed during the study period. Anti-TPO concentration was measured with ECLIA method. In line with the definition provided by the test manufacturer, anti-TPO concentration of >18 kU/l was considered positive. Clinically significant anti-TPO value was defined as >100 kU/l. When anti-TPO was positive, thyroglobulin antibody (anti-TG), TSH and free T4 were measured. All subjects had diabetes associated antibodies measured (IAA, IA2A, GADA, ZnT8A and ICA when one of the previous was positive). Statistical analysis was performed with Mann-Whitney U test, p<0.05 was considered statistically significant.

Results: Girls had a higher median anti-TPO concentration than boys (12 vs 11 kU/l, p=0.001). A positive anti-TPO concentration occurred in 32 subjects (20 girls), that is 14.2% of the cohort. Girls with a positive anti-TPO concentration had a higher median anti-TPO value than boys, but this was not statistically significant (27.5 vs 23.5 kU/l, p=0.495). Four subjects (1.8%) had anti-TPO levels >100 kU/l, suggesting a very likely autoimmune thyroiditis. Anti-TG was measured in 28 children (four lost to follow-up), it was remarkably risen (>100 kU/l) in five subjects, of whom three had a high anti-TG without a clinically significant anti-TPO rise. Thyroid function was normal for all of these children. Only one of the 32 subjects had a positive diabetes associated antibody – IAA.

Conclusion: Girls with HLA-conferred susceptibility to T1D had higher anti-TPO concentrations than boys. The prevalence of positive anti-TPO in our cohort was 14.2% which is remarkably higher than previously described prevalence in healthy children. All of the subjects had a normal thyroid function, therefore, in children with HLA-conferred susceptibility to T1D, routine anti-TPO measuring is not justified, at least up to the age of ten.

P1-290

Prediction of permanent and transient congenital hypothyroidism based on levothyroxine dosages in long-term follow-up patients: a multicenter retrospective study in Japan

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Background: Congenital hypothyroidism (CH) can be categorized into two types: transient CH (group T) and permanent CH (group P). Several studies have recently demonstrated that the levothyroxine (LT4) dosage is useful for predicting LT4 requirement; however, none of the studies followed up their patients to puberty.

Objective: To determine the cutoff value for the LT4 dosage as a predictor of LT4 requirement after puberty in patients with CH.

Methods: This was a multicenter retrospective study. After excluding patients with Down syndrome, among others, the LT4 dosage and clinical data of eligible patients with CH who were followed up at our hospitals from the neonatal period to ≥15 years of age were analyzed. The LT4 dosages at ages 1, 2, and 3 years were compared between the two groups, and receiver operating

characteristic analysis for the groups was performed to establish the cutoff dosages of LT4 at those ages. To determine the optimal cutoff values for clinical decision-making, further analyses were performed to identify the LT4 dosage with the highest specificity for groups P and T. Group P was further divided into two subgroups: permanent dysgenesis(PD) and permanent eutopic (PE). Group PD (n=29) included patients with thyroid dysgenesis, such as an ectopic thyroid gland, semilobar deficiency, or athyrosis.

Results: The subjects were classified into groups P (n=75), T (n=24), PD (n=29), and PE (n=46). The LT4 dosages were significantly higher in group P than in group T. The optimal cutoff values at 1, 2, and 3 years of age were 3.26, 2.29, and 2.32 µg/kg/day, respectively. At 1 year of age, higher LT4 dosages were required in group P than in group T (median 3.75 vs. 2.88 µg/kg/day; p < 0.001). When the LT4 dosage cutoff values at 1 year of age were set at 4.79 and 1.74 µg/kg/day, the specificities of P-CH and T-CH (for denying T-CH and P-CH, respectively) were 100% and 97%, respectively. The results between group PE patients and group T patients were not essentially altered. In patients with T-CH, LT4 re-administration was not introduced during the follow-up of ≥12 years after discontinuing LT4 treatment.

Conclusions: LT4 dosages >4.8 µg/kg/day and <1.7 µg/kg/day at 1 year of age may help predict P-CH and T-CH, respectively.

P1-291

An incidental finding of thyroid hormone resistance due to a de novo mutation in the *THRβ* gene

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Background: Thyroid hormone resistance (THR) is a rare genetic disorder that may be caused by thyroid hormone (TH) cell transporter defects or metabolism defects, but most cases are caused by an inherited mutation in the TH receptor beta (*THRβ*) gene. The reduced responsiveness of target tissues to TH is characterized by elevated TH and a normal or elevated thyroid-stimulating hormone (TSH) level. Differentiating between THR and TSH-producing pituitary tumors is challenging.

Patient and Methods: A previously healthy five-year-old boy was found to have elevated FT4 and FT3 (38.8 pmol/L (and 12 pmol/L, respectively)) with a normal TSH of 1.1 mIU/L, in a routine work-up. He had no symptoms or signs of hyperthyroidism. Anti-thyroglobulin, thyroid peroxidase and thyroid receptor antibodies were negative. Parents and three siblings were all found to have normal thyroid functions. To rule out a TSH-secreting adenoma performance of a brain MRI and a TRH test were considered. We decided to start with genetic testing. After proper consent, DNA samples were obtained from all six family members, and the *THRβ* gene was sequenced using Sanger sequencing.

Results: The proband was found to have a *de novo* mutation in one allele of the *THRβ* gene. The missense mutation, occurring in a CpG dinucleotide hot spot (C GAG), involves a single nucleotide substitution of an adenine for the normal guanine at codon 460, resulting in replacement of the normal glutamine with

a lysine (E460K). This mutation, previously described in 10 families, reduces the binding affinity for T3 to 25% that of the normal receptor. The mutation was not found in the other family members tested.

Conclusion: Thyroid hormone resistance should be considered in the differential diagnosis of patients with non-autoimmune, non-goiterous hyper-thyrotropinemia. Most patients are asymptomatic and elevated thyroid hormone levels could be an incidental finding. Although inheritance is autosomal dominant, normal thyroid function in the parents does not rule out the diagnosis because of the possibility of de novo mutations in the THRB gene. The main differential diagnosis to be considered is TSH-secreting adenoma. A fast genetic diagnosis can avoid an unnecessary, costly and complicated work-up, including brain MRI, which requires general anesthesia in small children. Accurate diagnosis is crucial to appropriate follow-up and genetic counseling.

P1-292

Outcome of congenital hypothyroidism in Algeria: the urgent need to implement a national newborn screening program

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Background: Congenital hypothyroidism (CH) is the commonest congenital endocrine disorder and the primary cause of treatable mental retardation. In low-income countries lacking newborn screening programs, CH remains a serious public health problem.

Objective: To investigate the characteristics at diagnosis and clinical outcome of patients with CH in Algeria; and determine factors related to psychomotor development.

Methods: A retrospective study of patients referred for elevated TSH between 2007 and 2017 was conducted in two pediatric clinics in Algiers. Age at diagnosis, clinical characteristics and initial dose of treatment were recorded. Patients were classified as having transient or permanent CH upon imaging and/or re-evaluation at 3 years. Severity was assessed according to venous free thyroxine (FT4) and thyroid stimulating hormone (TSH) at diagnosis. Neurocognitive assessment was based on intelligence quotient (IQ) evaluation using Weschler Preschool and Primary Scale of Intelligence III. Severe cognitive delay was defined as IQ below 70.

Results: Between 2007 and 2018, 139 patients (75 girls, 64 boys) were followed for a mean \pm SD (range) duration of 3.5 ± 2.5 [0.1-9] years. Mean age at diagnosis and start of treatment was 7.2 ± 16.3 [0.1-138] months. Consanguinity was present in 20(16%) of cases, with a family history of thyroid disease in 47 (34%) and there were 7 familial cases. The most common clinical feature was jaundice, seen in 49 (41%). Delayed development was found in 10 (7%) and short stature in 9(6%) patients, both associated with late diagnosis(>3 months of age). Of the 30 cases re-evaluated at 3 years, 13 (43%) had permanent hypothyroidism. TSH was higher

in permanent compared with transient CH, median TSH 125.6 vs 18.4 mUI/l ($p < 0.001$). Overall IQ in 43 children evaluated aged 6.6 ± 2.2 [2.5-10.8] years was 80.95 ± 17.8 [34-104]. IQ >80 was correlated with an earlier mean age at diagnosis: 2.4 ± 1.4 vs 13.3 ± 18.5 months $p < 0.0001$.

Discussion: Diagnosis of CH remains late in Algeria, with a correspondingly poor neurodevelopmental outcome. These data testify to the need to view newborn screening as an emergency in our country and in other African countries.

P1-293

Genetic susceptibility to Hashimoto's Thyroiditis in children: analysis of polymorphisms rs7093069 – IL2RA, rs5742909 – CTLA 4, rs7138803 – FAIM2

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Background: Hashimoto's Thyroiditis is influenced by genetic and environmental factors. Interleukin-2 receptor alpha chain (IL-2RA) gene polymorphism and Cytotoxic T-lymphocyte antigen 4 (CTLA 4) gene polymorphism are known to be associated with HT, but have not been established in a Caucasian children population yet. The Fas Apoptotic Inhibitory Molecule 2 (FAIM2) gene polymorphisms impact on the development of HT in children has not been reported yet.

Objective and Hypotheses: To estimate the association of polymorphisms of IL2RA, CTLA 4, FAIM2 genes with the predisposition to HT in children.

Method: The study was performed in 81 patients with HT and 160 healthy volunteers recruited from two endocrine centers from Poland and Italy. The three single nucleotide polymorphisms (SNPs): rs7093069, rs5742909, rs7138803 were genotyped by Taq-Man SNP genotyping assay using the real-time PCR.

Results: Rs7093069 C alleles were more frequent in patients with HT in comparison to healthy subjects ($p=0.035$ with OR=1,5). Rs5742909 C alleles were more frequent in HT patients in comparison to healthy subjects ($p=0.049$, OR=1,7). Rs7138803 A alleles were more frequent in HT patients in comparison to healthy subjects ($p=0.022$ with OR=1,5).

Conclusion: Rs7093069 C/T IL2RA, rs5742909 C/T CTLA 4, rs7138803 A/G FAIM2 polymorphisms could contribute to development of HT in children. The main risk factor for rs7093069 and for rs5742909 is C allele for rs7138803 A allele.

P1-294**Effect of serum TSH level on ovarian volume in prepubertal girls with subclinical hypothyroidism**

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Background and objectives: Enlargement and cystic changes in ovaries of patients with longstanding overt hypothyroidism has been observed in numerous case reports. But there is limited data about the effect of subclinical hypothyroidism (SH) on ovarian volume and ovarian cyst formation. We evaluated the relationship between serum thyroid stimulating hormone (TSH) level and ovarian volume and sonographic appearance in prepubertal girls with SH.

Material and Methods: Patients who were aged between 5-10 years and diagnosed as having SH (TSH>5 µIU/L and free thyroxine (fT4) normal) and had no history of chronic disease, use of medication that can effect thyroid functions along with age matched healthy euthyroid controls were enrolled in the study. Patients that have obesity or thyroiditis were not received to study. All patients were prepubertal (Tanner stage 1 breast development). Anthropometric (body weight, height and blood pressure) and laboratory (luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2) and thyroid function tests) measurements were performed. All patients underwent a detailed suprapubic pelvic ultrasonographic examination to evaluate the ovarian volume and ovarian cyst formation.

Results: Thirty-five children with SH (mean age; 7.6±1.0 years) and 50 healthy girls (mean age; 7.7±1.2 years, p=0.926) were enrolled in the study. Anthropometric parameters (height-SDS, weight-SDS, body mass index (BMI), BMI-SDS) of the groups were similar ($p>0.05$). TSH and LH levels were significantly higher in SH group than controls ($p<0.05$), however there was no significant difference between the two groups in terms of sT4, FSH and E2 levels ($p>0.05$). When the groups were compared in terms of ovarian volumes the right and left ovarian volume was significantly higher in the SH group ($p<0.001$). TSH was positively correlated with LH and ovarian volumes in patients with SH ($p<0.05$).

Conclusion: The results of this study showed that ovarian volumes of patients with SH were significantly greater than those with normal thyroid function. Although ovarian enlargement and cyst formation is well recognised in longstanding overt hypothyroidism, it has been shown for the first time in patients with SH.

Key words: subclinical hypothyroidism, puberty, ovarian volume

P1-295**The Natural History of Delayed TSH Elevation in Neonatal Intensive Care (NICU) Newborns**

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Context: Delayed TSH elevation (dTSH) is defined as elevated TSH in the second neonatal screen following normal TSH in the initial screen. The clinical outcome of newborns with dTSH is not entirely elucidated, although several studies have suggested a full recovery in most cases.

Objective: We aim to elucidate the natural history of dTSH in a group of neonatal intensive care newborns. In addition, we aim to define clinical and endocrine parameters that may predict the outcome of newborns with dTSH, *i.e.* transient vs. permanent hypothyroidism.

Design, Setting and Participants: An observational study was performed in a cohort of 113 children with a history of dTSH. Birth parameters, thyroid screening results, thyroid gland imaging, levothyroxine dose and neurological outcome were compared between newborns with spontaneous recovery and children with a final diagnosis of either transient or permanent hypothyroidism.

Results: 93% of the children with a history of dTSH demonstrated a recovery, either spontaneously or following levothyroxine treatment (transient hypothyroidism). Newborns with a spontaneous recovery demonstrated milder thyroid dysfunction on the newborn screening compared with newborns who started levothyroxine treatment. Levothyroxine dose was lower in children with transient vs. permanent hypothyroidism only during the first six months of life, but otherwise these groups were similar in birth parameters, thyroid screening tests and gland imaging. In spite of similar management, developmental delay was more common in children with permanent than transient hypothyroidism (71% vs. 17%, $p=0.01$). Duration of treatment was highly variable in children with transient hypothyroidism and ranged from several months to over three years.

Conclusion: Thyroid dysfunction is transient in most cases of dTSH. No reliable parameters can predict a-priori transient vs. permanent hypothyroidism, but the neurological outcome in the latter form is worse. A prospective study is required to define the earliest timing for a safe cessation of therapy in newborns with dTSH.

Adrenals and HPA Axis

P1-296

Three novel mutations of the StAR gene in five Algerian patients presenting with classical and non-classical lipoid adrenal hyperplasia

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Background: StAR deficiency is a rare cause of primary adrenal insufficiency (PAI), with fewer than 100 cases reported worldwide. The first patients to be described suffered from severe forms of lipoid adrenal hyperplasia leading to severe undervirilization in 46,XY foetuses. More recently, however, less severe forms, known

as “non-classical” or “atypical lipoid adrenal hyperplasia”, presenting with PAI with salt wasting (SW) syndrome and normal male genitalia have been reported.

Objective: To present clinical and genetic data in five patients from three families with StAR deficiency.

Methods: Clinical data were collected from all known patients with StAR deficiency. Parental consent was obtained for genetic analysis to be performed. Massively parallel sequencing (MPS) with a custom panel targeting candidate genes in adrenal insufficiency was carried out. Mutations identified by MPS were confirmed in patients and their parents by Sanger sequencing.

Results: Between 2011 and 2018, five patients, current median (range) age 2.6 (0.6-7.4) years were found to have StAR deficiency. Clinical and genetic data are summarized in the table.

Discussion: StAR deficiency is a rare but important cause of PAI. Diagnosis in the classic form presenting with severe undervirilization requires investigation of chromosomal sex and the presence of a uterus. However, the existence of atypical forms with normal or mild undervirilization underlines the importance of testing for genes involved with steroidogenesis, including *StAR*, in unexplained PAI.

Patient (Pt)	Pt1	Pt2	Pt3	Pt 4	Pt 5
Consanguinity	Yes	Yes	Yes	Yes	Yes
Family history of adrenal insufficiency	Sister died at 2 months (SW)	Brother (Pt3)	Sister (Pt2)	Brother (Pt 5)	Sister (Pt4)
Age at presentation	23 days	5 months	1 day	19 months	24 months
Mode of presentation	SW	SW	Family history and DSD	SW Pigmentation	SW Micropenis
External genitalia	Female	Female	Ambiguous	Female	Male Micropenis
Length(cm) of cliterophallus	<0.5	<0.5	1	<0.5	1
Testes	Inguinal folds	No	Inguinal folds	No	Scrotal
Uterus	No	Yes	No	Yes	No
Karyotype	46,XY	46,XX	46,XY	ND	ND
Sex of rearing	Female	Female	Male	Female	Male
Na/K (meq/l) at diagnosis	114/5.2	121/5.6	140/3.7	137/4.7 (on treatment)	126/6
ACTH (pg/ml)	1403	677	387	2000	2090
Renin (pg/ml)	76.8	8634		251	71180
Testosterone (nmol/l)	<0.05		0.41		
AMH (pmol/l)	359	-	209		
StAR gene mutation (homozygous)	c.306+2dup T in intron 3	c.64+480_c.167del in exon 2	c.64+480_c.167del in exon 2	c.73T>A p.Leu8Gln	c.73T>A p.Leu8Gln

P1-297**A novel compound heterozygous mutation in the CYP11B2 gene, including an intron 7 splice site, is responsible for aldosterone synthase deficiency type II**

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Objective: To investigate the clinical and molecular characteristics of a girl with aldosterone synthase deficiency type II (ASDII). We also identified the consequences of a novel splice site mutation in the CYP11B2 gene.

Materials and Methods: A 4-month-old girl presented with vomiting, diarrhea, and failure to thrive. Her 17 α -OHP, cortisol, renin, and aldosterone were all in the normal range, and the ACTH stimulation test suggested that the adrenal cortex responded well. Sequencing was performed using genomic DNA. An in vitro analysis was performed using a minigene splicing assay based on the pSPL3 exon trapping vector. The wild-type (pSPL3-WT) and mutant (pSPL3-Mut) plasmids, containing exon 7, intron 7, exon 8, a partial sequence of intron 6 and intron 8, were separately cloned into the pSPL3 vector. The wild-type and mutant constructs were transiently expressed in COS-7 cells. Cellular RNA was extracted for reverse transcription, and the PCR products were sequenced for further identification. Structural simulation of the two novel mutations was conducted.

Results: The mutation analysis identified one patient with compound heterozygosity [c.1342C>T/pR448C; c.1200+1G>A/p.L375Cfs*1]. The minigene construction analysis revealed that the mutation resulted in aberrant splicing, in which exons 7 and 8 were skipped, resulting in the deletion of exons 7 and 8 and the premature formation of a stop codon in exon 9.

Conclusion: We report two novel CYP11B2 mutations in a Chinese family with ASD type II. We identified one splice mutation (c.1200+1G>A/p.L375Cfs*1). The description of the metabolic phenotype of the patient is important for clinician. A genetic test is an effective diagnostic tool for rare endocrine-metabolic diseases.

P1-298**First morning pregnanetriol and 17-hydroxyprogesterone correlated significantly each other with in 21-hydroxylase deficiency**

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Background: Biochemically monitoring 21-hydroxylase deficiency (21OHD) treatment is challenging. Serum/blood 17-hydroxyprogesterone (17OHP) measurements, especially in the early morning before medication, are traditionally used for this purpose. Urinary pregnanetriol (PT), a urinary metabolite of 17OHP, may also be used. Based on auxological data, we previously reported that the first morning PT value in the range of 2.2–3.3 mg/gCr is optimal for monitoring 21OHD treatment. No report thus far has compared urinary PT and 17OHP values.

Objective: To explore the correlation between first morning urinary PT value before glucocorticoid administration (0h-PT) and the serum/blood 17OHP value at three time points, namely, before (0h-17OHP) and two and four hours after glucocorticoid administration (2h-17OHP, 4h-17OHP).

Design: This was a prospective study done at two children's hospitals.

Methods: In total, 24 patients with 21OHD aged 3–25 years were recruited. The urinary PT levels and 17OHP levels were measured for three days within a week. The 0h-PT (n=69) values were collected on all three days. Enzyme immunoassay (ELISA) of dried blood spots (DBS) was done for 2h-17OHP (n=22) and 4h-17OHP (n=22) on day 1 and for 0h-17OHP on days 2 and 3 (n=45). Serum 17OHP levels were also measured on day 1 by ELISA and LC-MS/MS (n=24).

Results: All 24 patients received both gluco- and mineralocorticoids. The 0h-PT value for the total samples was 0.12–56.1 mg/gCr (n=54). DBS 0h-, 2h-, and 4h-17OHP levels were 0.28–100, 0.44–77.1, and 0.54–87.2 ng/ml, respectively. A significant, positive correlation was found between the 0h-PT and DBS 0h-17OHP values ($r=0.961$, $p<0.01$), but none was observed between the 0h-PT and DBS 2h- or 4h-17OHP values. When the 95% confidence intervals of the mean 0h-PT level obtained during a period of good disease control (2.2–3.3 mg/gCr) in our previous study were applied, the DBS and serum ELISA for 0h-17OHP yielded a value of 14.2–19.1 ng/ml and 29.5–37.2 ng/ml, respectively. The day-to-day variation in 0h-PT (n=51) was 24.7 ± 22.3%. We confirmed a significant correlation between ELISA and LC-MS/MS in terms of 17OHP level.

Conclusions: First morning PT correlated significantly only with DBS 17OHP before morning medication. Since early morning serum/blood 17OHP measurements are impractical for patients and caregivers and the levels do not reflect a long period of disease control, first morning PT measurements may be more useful for biochemical monitoring of 21OHD.

P1-299

Medical identification jewellery use in children and young adults with adrenal insufficiency

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Background: Adrenal insufficiency (AI) is a rare disorder in the paediatric population. Patients are at risk of an adrenal crisis (AC), which comprises hypotension, acute abdominal symptoms, reduced consciousness, hypoglycaemia, hyperkalaemia and hyponatraemia. Immediate administration of parenteral hydrocortisone is essential to prevent AC progression but delays may occur when health attendants are unaware of the underlying AI diagnosis. Medical jewellery is a non-verbal way of communicating an AI diagnosis in an emergency. It provides medical information on a recognisable emblem attached to a bracelet or necklace and additional information is available via telephone. While use of such a service is recommended, the extent which it is adopted by patients is unknown.

Aim: The aim of this study was to assess the use of medical jewellery among patients aged 25 years and under with AI in Australia.

Methods: Data on the age, sex, diagnosis and treatment for each eligible subscriber were extracted from the largest medical jewellery database on 17 September 2018. Subscription rates were calculated using 2017 Australian population data.

Results: There were 666 patients with AI in the database but only 358 (53.8%) had an active (up to date) subscription, corresponding to a subscription rate of 43.7/million or approximately 14.6% of the estimated patient population. The majority (66.5%, n=238) had primary AI; 82 (22.9%) had secondary AI; and 38 (10.6%) patients could not be classified. Congenital adrenal hyperplasia (CAH) was the most frequent diagnosis (n=153, (42.7%)), corresponding to a subscription rate of 18.7/million or 28.9% of the estimated number of patients with CAH. The mean age of subscribers was 15.9 (SD=5.8) years, with only 18 (5%) patients aged under 5 years. More females (n=199, 55.9%) than males were active subscribers and subscription rates differed significantly by geographic area. Inactive (lapsed) subscriptions increased with age and were highest in the 20-25 year age group.

Discussion: This is the first study examining the uptake and maintenance of a medical jewellery subscription service in young people with AI. Utilisation was lower than recommended. Uptake increased with age but was associated with higher levels of lapsed subscriptions. Females used jewellery more than males. Geographic differences suggest that local factors also influence subscribing. High levels of lapsed subscriptions indicate the need for ongoing reinforcement of AC preventive education.

P1-300

Growth trajectory and final height in children with non classical congenital adrenal hyperplasia

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Background: Subjects with non classical congenital adrenal hyperplasia (NCCAH) often present an increased growth velocity secondary to elevation of adrenal androgens that promote early bone maturation and compromise final height (FH). The aim of the study was to analyze prognostic factors affecting growth trajectory and FH in children with NCCAH.

Design: retrospective, multicentric study

Study Population: 192 (140 females) NCCAH children with confirmed molecular diagnosis followed from diagnosis up to FH.

Methods: clinical records were collected and analyzed. The study population was divided for gender, with or without hydrocortisone treatment (171 treated with hydrocortisone) and type of the mutation of CYP21A2 gene (V281L homozygosity in 55, compound heterozygosity with V281L in 85 and other mutations in 48 cases).

FH (SDS), pubertal growth (PG) (cm), growth trajectory (GT) since diagnosis to FH (SDS) and FH adjusted to target (TH) (FH-TH)(SDS) were evaluated as outcomes using stepwise linear regression models.

Results: FH SDS and FH-TH were not significantly different in both gender (-0.34 vs -0.36, p =0.98 and -0.05 vs 0.05, p=0.65, respectively).

At stepwise linear regression analysis, FH and FH-TH resulted significantly related to chronological age (CA) (p= 0.008 and 0.016), bone age (BA) / CA ratio (p= 0.004 and 0.001), height (H) (p=0.000 for both parameters) at NCCAH diagnosis and TH (p=0.013 and 0.000) .

PG was higher in males (22.59 ± 5.74 vs 20.72 ± 17.4 cm in females, $p=0.002$), as physiologically observed, and was positively related to H ($p=0.027$), negatively to BMI ($p=0.001$) and BA/CA ratio ($p=0.001$) at NCCAH diagnosis.

The type of the mutation of CYP21A gene and hydrocortisone doses did not influence significantly the parameters of growth of our NCCAH patients.

The comparison between treated with hydrocortisone and untreated patients did not evidence significant differences on GT, but the statistic value of these results is limited by the small number of untreated group.

Conclusion: FH and GT of NCCAH patients is significantly influenced by auxological parameters at diagnosis (CA, BA/CA ratio, H). Gender, molecular alteration, biochemical picture and hydrocortisone doses seem to have no important influence on height outcome of these NCCAH children.

P1-301

Height in Infants aged 1 year with classic Congenital Adrenal Hyperplasia is related to their urinary Steroid Metabolome

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Background: Controlling therapy of infants, especially from neonates onwards, with classic congenital adrenal hyperplasia (CAH) is challenging due to the lack of reference values.

Methods: We retrospectively analyzed 158 spot urinary steroid hormone metabolite profiles determined by gas chromatography-mass spectrometry (GC-MS) of 60 infants aged 0–4.2 years with classic 21-hydroxylase deficiency (21-OHD) on hydrocortisone and fludrocortisone treatment.

Results: Infants aged 1 year (N=14) demonstrated a reduction of their height (H-SDS: -1.0 ± 1.7). H-SDS was significant negatively correlated with tetrahydrocortisol (THF) to tetrahydrocortisone (THE) ratio ($R_s = -0.70$; $P < 0.01$), demonstrating an impact of the individual metabolism of hydrocortisone on growth. Additionally, H-SDS was negatively correlated with the ratios of THF-to-pregnane triole ($R_s = -0.64$; $P = 0.02$), THF-to-11-hydroxyandrosterone ($R_s = -0.66$; $P = 0.01$), and the ratio of THF-to-summed-androgen-metabolites (androsterone, etiocholanolone and 11-hydroxyandrosterone) ($R_s = -0.71$; $P < 0.01$). Infants with H-SDS < -1 had significant higher ratios than those with an H-SDS > -1 . In contrast, the hydrocortisone dosage was not related to H-SDS.

Conclusion: A substantial proportion of infants with CAH were over treated. The urinary steroid hormone metabolite profiles, but not the prescribed hydrocortisone dosage, were related to height in infants with classic CAH. Additionally, the individual metabolism of hydrocortisone, as shown by the tetrahydrocortisone to tetrahydrocortisol ratio, influences the growth in infants treated with hydrocortisone.

P1-302

MIRAGE syndrome, a novel syndromic form of primary adrenal insufficiency

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Primary adrenal insufficiency (PAI) is a rare but potentially life-threatening disease. When this happens very early in life, genetic causes should be considered. Here, we report a newborn who presented with hyperkalemia, hyponatremia, hypoglycaemia and generalised hyperpigmentation, and was found to have primary adrenal insufficiency. This child also had concurrent issues of poor growth, sepsis and persistent pancytopenia. She was eventually diagnosed with MIRAGE syndrome (Myelodysplasia, Infection, Restriction of growth, Adrenal hypoplasia, Genital anomalies and Enteropathy) following the detection of a germline de-novo likely pathogenic variant in *SAMD9* (c. 3406G>C; p. Glu1136Gln).

In addition to providing an update on this novel syndrome form of PAI, this report highlights the value of advanced genetic workup of PAI in providing a definite diagnosis to facilitate management and counselling.

P1-303

Hypothalamo-pituitary-adrenal (HPA) axis in infants exposed to corticosteroids during fetal life

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Background: Prednisolone, prednisone, and hydrocortisone, are used during pregnancy, in women with thrombocytopenia, auto immune or inflammatory diseases. The current belief speculates on the absence of adverse effects on the hypothalamo-pituitary-adrenal (HPA) axis of the fetus, thanks to placental 11BHSD2 inactivation.

Objective and Hypotheses: We analyzed the results of ACTH tests routinely performed in neonates exposed in utero to corticosteroids during fetal life, with the hypothesis that HPA function would be normal in most cases.

Patients and Methods: We retrospectively collected all ACTH tests performed from 2012 to 2018 in neonates exposed in utero to corticosteroids, in our laboratory database. Twenty six files were retained for analysis. The infants had ACTH tests in the first 15 days of life and then every two months until HPA axis recovered. Meanwhile they had adequate glucocorticoid replacement in case of stress.

Results: Twenty-one mothers (80.8%) received prednisone, two (7.7%) prednisolone, and three (11.5 %) hydrocortisone. Mean dose of the treatment was 44 mg/day (2.5-80) and mean duration was 78 days (7-272). Mean cumulative dose was 1370 mg

(525-4680). Six (23.1%) women received over 60 mg/day for at least two weeks, and eight (30.1%) were treated for more than 100 days. Mean Z-score at birth was -0.29 SDS for weight, -0.49 SDS for length and -0.43 SDS for head circumference. Three (12.5%) were born small for gestational age, and three had transient hypoglycemia. Twenty neonates (76.9%) had an abnormal first ACTH test. The cumulative dose of 1300 mg was the threshold, beyond which all children had a low abnormal response (n=7), but no least dose was safe. The result of the ACTH test was not correlated to the cumulative dose, or to the duration of the exposition. At mean age of two months, 19 infants had a second ACTH test with a low response in nine cases. Six were tested again, of which five had a normal ACTH test at the mean age of 4.4 months and a last child at 5.5 months. The mean delay to recover a normal HPA function was 76 days.

Conclusion: We found a surprisingly high amount of HPA axis anomalies (76.9 %) in neonates exposed during fetal life to corticosteroids. Although rare, acute adrenal insufficiency has been reported in this situation. We propose to educate caregivers and parents to adequate stress glucocorticoid replacement in the first months of life. These results should be confirmed by a large prospective study.

P1-304

Identification of novel and rare CYP21A2 variants in Chinese patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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Objective: 21-hydroxylase deficiency (21-OHD) is the most common cause of congenital adrenal hyperplasia due to CYP21A2 gene mutation. The aim of study is to expand CYP21A2 mutational spectrum in the Chinese population and to provide novel genetic information in terms of ethnic diversity.

Methods: 95 Chinese suspected 21-OHD patients with phenotypes varying from salt-wasting (SW) to nonclassic symptoms were recruited. The clinical characteristics were retrospectively analyzed. Sanger sequencing and multiplex ligation-dependent probe amplification were used to detect point mutations and large gene deletions, respectively.

Results: 20 different mutant alleles were detected in 35 patients with 21-OHD. The most common variant was c.293-13A/C>G (30.0%), followed by p.I173N (20.0%), large gene conversions (14.3%), large gene deletions (11.4%), and p.R484Pfs*58 (4.3%). Remarkably, we identified a novel F450L variant, *in silico* predicted to be associated with the salt-wasting form. Two variants including p.R409C and p.R427H, previously considered as conserved in specific ethnicities due to a founder effect, were detected in our cohort. Further, a rare p.H63L+p.V70L variant, hitherto only observed in the Chinese population, *in trans* with different variants corresponding to the salt-wasting form resulted in diverse phenotypes.

Conclusions: One novel and four rare variants of CYP21A2 gene corresponding to severe phenotypes were identified in our cohort. Two variants including p.R409C and p.R427H have wider

ethnic distributions. Therefore, the sequence of CYP21A2 gene must be analyzed carefully in case rare or novel deleterious variants exist. Our findings improve the understanding of CYP21A2 mutational spectrum in 21-OHD patients and contribute to the precise diagnosis and prenatal counseling.

P1-305

Clinical Manifestations & Molecular analysis of four Palestinian patients with Pseudohypoaldosteronism type 1 (PHA 1) revealing Four novel mutations in the ENaC subunit genes

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Objectives: Pseudohypoaldosteronism type 1(PHA 1) is a rare hereditary disorder characterized by resistance to the actions of aldosterone. Two different modes of inheritance with different mechanisms and clinical manifestations have been described , Autosomal recessive that affects the epithelial sodium channel (ENaC),the defect is permanent and affects all aldosterone target organs. Autosomal dominant or sporadic PHA 1, affects the mineralocorticoid receptor in most patients.

Methods: Four unrelated Palestinian infants to a consanguineous Palestinian families presented in the first week of life with severe dehydration, hyponatremia, hyperkalemia and severe metabolic acidosis, assessed to have pseudohypoaldosteronism and were managed with hypertonic saline and kayexalate, and did not improve on mineralocorticoids. Plasma renin activity & Aldosterone levels were extremely elevated.

Results: Whole exom sequencing and subunit genes of the ENaC were sequenced and revealed four novel mutations, R73C (Arg73Cys)mutation in the SCNN1A gene in one patient, c.142-143insC mutation that leads to frameshift and premature stop codon(p.S47fsX69) of SCNN1G gene in another patient, c.69delG causing frameshift and stop codon (p.G23GfsX26) of SCNN1A in another patient and G315R (Gly315Arg) in exon 6 of codon 315 of SCNN1B gene.

Conclusions: To our knowledge, this is the first description of this disease in a Palestinian family with molecular confirmation, allowing accurate genetic counseling, early diagnosis of affected kindreds, early therapeutic interventions and avoiding complications and checking if the clinical presentation does correlate well with the specific genotype.

P1-306**Genotype-Phenotype Correlation and Clinical Findings in 145 Patients with Congenital Adrenal Hyperplasia: Single Centre Experience**

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Introduction: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders of adrenal steroidogenesis.

Aim: The purpose of this study was to investigate genotype-phenotype correlation, clinical findings and long-term outcomes in patients with CAH due to 11 β -hydroxylase deficiency (11 β -OHD) and 21-hydroxylase deficiency (21-OHD).

Patients and methods: 145 genetically proven 21-OHD and 11 β -OHD patients were included in this study. Endocrinological, clinical and molecular findings were recorded at presentation and follow-up.

Results: Out of 145 patients diagnosed with CAH, 122 had (83.6%) 21OHD[66 salt wasting (SW), 40 simple virilizing(SV), 16 non-classic(NC)]; 23(16.4 %)had 11 β -OHD. SW 21-OHD was the most common and the earliest diagnosed CAH type. Consanguinity rate was high in all groups. Due to severe virilization and late diagnosis, some of the XX patients were raised as male. Frequency of SGA was higher in SV and NC 21-OHD($p=0.048$). While 29 different mutations were detected in 21 OHD, there were 12 different mutations in 11 β -OHD. The most common mutation was IVS-2 not only in the all patients with 21-OHD, but also in the SW(34.7%)and SV(34.4%). Furthermore, the most common mutation in NC 21-OHD was p.V282L(34.4%) and p.Leu299Pro(25%) in 11- β OHD. Positive predictive value(PPV) for all 21-OHD patients was 78.4%. PPV in subgroups(according to enzyme activity) was 80.8% in group0 ('Null'=Enzyme activity:0%), 100% in groupA(1%), 62.5% in groupB(1-2%), and 65.2% in groupC (20-50%). There was no genotype-phenotype correlation in patients with 11- β OHD. Mean value of the difference between the adult height and the target height for those, who have reached adult height was -0.42 ± 0.73 in SW; -0.91 ± 1.35 in SV, -0.14 ± 0.94 in NC, and -0.71 ± 1.43 in 11- β OHD. The pubertal spurt was not sufficient in classic 21-OHD. The rate of early puberty was 24.2% in SW, 40% in SV, 18.8% in NC 21-OHD and 56.5% in 11- β OHD($p=0.003$ in all groups). Frequency of testicular adrenal rest tumour (TART) was 29.4% for SW, 33.3% for SV and 40% for 11- β OHD. While the obesity rate in all subgroups of 21-OHD(32.8% in SW,33.3% in SV, 31.2% in NC) was significantly high, it was low in the 11- β OHD (5%)($p=0.010$).

Conclusion: In Turkey the rate of 11- β OHD was high. The rate of mutation diversity for both 21-OHD and 11- β OHD was very high. The positive predictive value of genotype-phenotype correlation in 21-OHD was good. Detection of the frequency of mutations may be important for early diagnosis, prenatal diagnosis and treatment, and establishing a screening strategy.

P1-307**"CAH-X" due to homozygous deletions of CYP21A2 and TNXB exon 35 in a newborn from the 17 OHP screening**

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The CYP21A2 and the TNXB genes are highly homologous with their corresponding pseudogenes (CYP21A1P and TNXA), leading to frequent homologous recombination. The TNXB includes 43 exons, the mRNA encodes tenascin-X (TNX), an extracellular matrix glycoprotein, highly expressed in connective tissue.

CAH patients with a "contiguous gene syndrome" comprising a deletion of both genes- CYP21A2 and TNXB have been described. Chimeric genes generated by large gene deletion or gene conversion events, account for 20%-30% of the common CYP21A2 pathogenic variants in CAH patients. Nine CYP21A2/CYP21A1P (CH-1 to CH-9) and one TNXA/TNXB chimera have been described. TNXA/TNXB CH-1 resulted in a contiguous CYP21A2 and TNXB deletion. TNXA/TNXB CH-1 is characterized by a 120-bp deletion crossing exon 35 and intron 35 carried over from the TNXA pseudogene.

We present a newborn with extremely severe phenotype, with lethal outcome despite early hormonal substitution. He was born after 3rd pregnancy, at term, (BW 3100g, BL 50 cm, HC 34 cm, vaginal delivery). Severe bradycardia and bradypnea lead 8 hours later to intubation. Early hypoglycemia, hyponatremia and hyperkalemia were present, therefore methylprednisolone (GCS) was instituted early. Screening was taken on d 3, the extremely elevated 17 OHP results (>324 nmol/l) were reported immediately, 9-alfa fludrocortisone (MCS) was added (d 9) to the GCS and fluid therapy. The patient was transferred to a tertiary neonatology center (d10) with weight loss (9.7%), respiratory insufficiency, reduced muscle tonus and activity, marked hyperpigmentation, descended testis, elevated CRP, direct hyperbilirubinemia (316 mcmol/l, dBili 228), negative in the TORCH&hepatitis screen, with opened fetal communications, small left/right shunt, aneurism fossa ovale, left sided severe hydronephrosis, enlarged adrenals, no signs of atresia of the extrahepatic bile duct system, hypocholic stools and dark urine. The further clinical course was not typical for a newborn with classical CAH on therapy. The molecular genetic analysis (SANGER sequencing and MLPA) revealed homozygous

deletions in *CYP21A2* gene and its substitution with *CYP21A1P* pseudogene and chimera gene *TNXA/TNXB* at the intron - exon 35 boundary of the *TNXB* gene. The skin elasticity, the hypermobility of the joints and the aneurism fossa ovalis is in line with the Ehler Danlos syndrome phenotype, but due to the small age of the patient could not be further explored. The patient represents a case of *TNXA/TNXB* CH-1 with extremely complex phenotype and Ehler Danlos symptoms, adding to the phenotype of the contiguous CAH syndrome and additional *TNXB* – related diseases.

Diabetes and Insulin

P1-308

ABCC8 MODY in an Obese Adolescent Misdiagnosed with Type 2 Diabetes

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Introduction: An activating mutations in the *ABCC8* gene cause both transient and permanent neonatal diabetes mellitus (DM) or MODY 12. In relation to the variant in the *ABCC8* gene, patients may also present with either neonatal hyperinsulinism and/or DM later in life. Besides, the same variant can cause different phenotypic features among family members. Response to the sulfonylurea treatment may vary between patients.

Aim: To present the clinical features and response to sulfonylurea treatment in an obese adolescent misdiagnosed with type 2 DM, who was later found to have a heterozygous variant in the *ABCC8* gene.

Case: A 13-year-old girl was admitted to the endocrinology clinic because of hyperglycemia. At presentation, she had no polyuria, no polydipsia or weight loss. Her birth weight was 4500 g and no medical record of hyper or hypoglycemia in the neonatal period was present. Her father, mother and grandmother were diagnosed with DM and received insulin or oral antidiabetics. Her weight was at +3.43 SD, height at +1.22 SD, BMI was 30.3 kg/m² (+2.63 SD); she had Tanner stage V puberty and acanthosis nigricans. Fasting blood glucose 332 mg/dL (N, 60-100), insulin 37.4 mIU/mL (N, 2.6-24.9), C-peptide 5.69 ng/mL (N, 0.9- 7.1), HbA1c 10.4% (N, 4-6), diabetes autoantibodies were negative and ketonuria or acidosis on blood gas analysis were absent. The patient was diagnosed with type 2 DM, thus metformin (2 x 1000 mg) and low dose insulin glargine (0.25 U/kg/day) were administered. Because of ongoing hyperglycemia and elevated HbA1c level at follow-up, insulin aspart was initiated. Due to the remarkable family history of DM in three generations, negative diabetes antibodies and continuing insulin requirement, MODY was considered. A next generation sequencing of MODY genes (*GCK*, *HNF1A*, *HNF1B*,

HNF4A, *KCNJ11*, *INS* and *ABCC8* genes) revealed a previously identified heterozygous variant c.1252 T> C in the *ABCC8* gene. The mother was heterozygous for the same variant. A trial with sulfonylurea (gliclazide) was initiated and increased, while insulin aspart was discontinued. The patient is currently being treated with gliclazide (120 mg/) and insulin glargine (0.7 U/kg/d).

Conclusion: Molecular genetic analyses of MODY genes in patients with apparent type 2 DM, who have a strong family history of DM and on-going need for insulin treatment, may provide accurate diagnosis. In these cases, transition from insulin to sulfonylurea therapy may allow better glycemic control and improvement in the quality of life.

P1-309

Level of glycemic control in pediatric patients with type 1 diabetes in Bern: a cross-sectional study

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Background: Good glycemic control prevents long-term complications of microvascular and macrovascular diseases in type 1 diabetes (T1DM).

We aimed to investigate whether our patients had A1c values <7.5% as recommended by ISPAD and how therapy modality, duration of diabetes and pubertal status affected the metabolic control of our patients. We also set out to compare our quality of care with our results of 2008 and with other published data.

Methods: In 2017/18, we enrolled all patients with T1DM who were followed by the outpatient clinic of the University Children's Hospital Bern over a period of 6 months in an observational cross-sectional study. Each patient was assessed once during the observational period, including demographic and clinical data (sex, age, diabetes duration, pubertal status, insulin treatment modality, use of continuous glucose monitoring (CGM), A1c levels).

Results: 160 patients participated in the study, 41% (n=68) were boys and 49% (n=72) were girls. Patients had a mean age (SD) at time of visit of 12.6 (3.5) years (range 2-17 years) and a mean duration (SD) of diabetes of 4.6 (3.6) years (range 1-16 years). Most patients, 63% (n=100) received functional insulin treatment, 29% (n=47) used insulin pump and 8% (n=13) injected insulin on multiple times per day (twice-daily/three-dose). CGM devices were used by 43% (n=68) of patients in their diabetes management. Mean A1c was 8% and 71% had A1c >7.5%. Compared to results from our hospital from 2008, A1c was slightly higher (8% vs 7.6%), but more patients had diabetes for >2 years (80% vs 47%). Patients with T1DM duration >2 years had more often A1c levels above 7.5 % than patients with duration <2 years (p<0.001). A1c values were significantly lower (p<0.05) in patients using CGM devices (7.8% vs 8%). A1c values did not differ between prepubertal and pubertal patients or insulin treatment modality (functional insulin treatment, insulin pump or multiple daily injections).

Conclusion: The overall glycemic control was poorer 2017/2018 than in our study from 2008. This may be due to the higher percent of patients with diabetes duration >2 years, thus with more patients out of the remission phase. Patients wearing CGM devices performed better. Unfortunately, our patients in Bern did not reach the target A1c set by ISPAD, similar to results of other diabetes centres in Europe and the United States. This highlights the importance of regular consultations and extended use of CGM.

P1-310

Preliminary results of public health prevention program for diabetic ketoacidosis in children and adolescent

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Objectives: Diabetic ketoacidosis (DKA) is the leading cause of mortality in a type 1 diabetic mellitus (T1DM) in pediatric population. The prevalence of the DKA in the developed world ranges from 15% to 61% and in Croatia it is 33 to 36%. In the past few decades in Europe there have been no significant changes in the prevalence of DKA in patients with newly T1DM. In the previous preventive program known as the “Parma campaign”, which was conducted between 1991 and 1998 and reduced the prevalence of DKA from the initial 78% to the cumulative prevalence during the campaign of 12.5%. The aim of the prevention program was to reduce the prevalence of DKA in the Southern part of Croatia in children and adolescents with newly diagnosed T1DM.

Methods: Prevention program was started in April 2017 and consists of a series of activities (lectures, TV shows, social networking, public posters, free phone line) aimed to educate the entire public, primarily children and adolescents, parents, employees in pre-school and school facilities and medical workers. The study included 37 children and adolescents with newly diagnosed T1DM during the prevention program period from 1 April 2017 to 31 December 2018 and control group of 54 children and adolescents with newly diagnosed T1DM before prevention program from 1 January 2015 to 31 March 2017. DKA was defined according to ISPAD guidelines from 2018.

Results: The prevalence of DKA in the pre-campaign period was 33.33% while in the period during the campaign was 24.3%. There was no significant difference in age (8.82 ± 4.82 vs. 9.48 ± 4.25 years, $P = 0.504$) and gender (31 (57.4%) male and 23 (42.6%) female vs. 27 (73%) male vs. 10 (27%) female, $P = 0.129$) between before and during prevention program. Fasting glucose significantly lower during the prevention program (29.28 ± 10.7 vs. 24.9 ± 9.59 mmol/L, $P < 0.05$), while fasting c-peptide was significantly higher during the prevention program (0.23 ± 0.16 vs. 0.35 ± 0.31 nmol/L, $P < 0.05$).

Conclusion: In conclusion, this study demonstrated a positive trend in reduction of DKA in children and adolescents with newly diagnosed T1DM during the preventive campaign. However,

additional studies with long term follow-up are needed to further clarify the impact of public health prevention program on prevalence of DKA.

P1-311

Optimisation of transfection methods using DNA, RNA and Protein Formats for CRISPR Cas9 mediated gene knock out in Beta-TC-6 cells

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Background: Beta-tumour cells (β TC) are a group of highly differentiated beta cell lines derived by expression of the SV40 T antigen (Tag) oncoprotein under control of the insulin promoter in transgenic mice. β TC-6 cells exhibit glucose stimulated insulin secretion which makes them a valuable tool in understanding the mechanisms that regulate insulin secretion.

The CRISPR/Cas9 genome-editing platform is a versatile and powerful technology to efficiently create genetically engineered living cells and organisms. This system requires a complex of Cas9 endonuclease protein with a gene-targeting guide RNA (gRNA) to introduce double-strand DNA breaks (DSBs) at specific locations in the genome which are repaired by Non-Homologous End Joining (NHEJ) pathway, resulting in insertions and/or deletions (indels) which disrupt the targeted locus. The success of CRISPR genome editing experiments is limited by the intracellular delivery and expression of Cas9 protein and gRNA.

Aims: The aim of the project was to identify the optimal transfection conditions for the intracellular delivery of Cas9 protein and gRNA in β TC-6 cells so as to create a KO mouse cell model of Congenital Hyperinsulinism(CHI). Such cellular models would play a key role in the elucidation of the function of the two genes of interest- ABCC8 and HADH.

Methods: Several CRISPR sgRNAs were designed to target each gene and tested to identify the best sgRNAs to generate the KO cellular models. Optimisation of the delivery of CRISPR/Cas9 system included the evaluation of different formats such as plasmid DNA, mRNA and RNP complex using a reporter gene.

We performed transfections using different combinations of molecules including: plasmid DNA, Cas9 protein and gRNA in an RNP format to maximize targeting of the *Abcc8* and *Hadh* gene in β TC cells. A reporter (GFP) was initially used to evaluate the transfection efficiency of the plasmid DNA and mRNA with flow cytometry and fluorescent microscopy being used to detect the GFP signal. To obtain the highest transfection efficiency, transfection conditions were optimised by varying Beta-TC-6 cell density and amount of transfection reagent. For the delivery of Cas9/gRNA as an RNP format, different non viral vectors including Lipofectamine and nanocomplexes were used. At the molecular level, the disruption of the gene was confirmed by Sanger sequencing and T7 ENDO assay.

Results: Progress so far has addressed the optimisation of transfection conditions to deliver CRISPR/Cas9 in BTC6 cells.

P1-312

Treatment of diabetic ketoacidosis with sub-cutaneous regular insulin in non-ICU setting is economical and results in rapid recovery

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Diabetic ketoacidosis(DKA) is a potentially fatal complication in patients with type 1 diabetes mellitus(T1DM). The mainstay of treatment for DKA is correction of dehydration and correcting hyperglycaemia with insulin. Intravenous(IV) insulin is preferred over subcutaneous(SC) insulin as onset of action is rapid and the dose can be titrated based on blood glucose.

Aims: To compare efficacy and hospitalisation cost of subcutaneous insulin therapy to intravenous insulin infusion in treatment of DKA in children admitted at G. Kuppuswamy Naidu Memorial(GKNM) Hospital, Coimbatore, India.

Methods: Retrospective cohort study undertaken on children admitted with DKA from 2013-2017.

Groups Analysed: one cohort treated with IV infusion of regular insulin in ICU and another cohort treated with SC regular insulin in paediatric general wards.

Main Outcomes: overall cost of hospitalisation and hours to improvement.

Analysis: by independent samples T-test with SPSS software.

Results: 49 patients admitted with 51 episodes of DKA were analysed. Baseline characteristics of two groups were similar for age($p=0.68$) and sex($p=0.62$). Glucose($p=0.47$) and HbA1c($p=0.91$) at arrival were comparable. Proportion of girls:boys in either group was 14:8(IV insulin group) and 20:9(SC insulin group). Lowest pH recorded in children treated with IV insulin infusion was 6.822(range 6.822-7.154) and lowest pH in children treated with SC insulin was 6.831(range 6.831-7.292). Mean pH in SC group was 7.1 ± 0.12 and 7.00 ± 0.10 in IV group(p value=0.02).

29 episodes were treated with SC insulin and 22 episodes were managed with IV insulin infusion. 23% of patients had severe DKA, 52% had moderate DKA, and 25% had mild DKA.

Mean time to improvement in SC insulin group was 17.23 ± 9.85 hours and 34.95 ± 14.05 hours in the IV insulin infusion group($p=0.001$).

Average total cost of hospitalisation was Indian Rupees 53712 ± 18813 for the IV group and 14369 ± 5768 for the SC group($p=0.000$). Total daily dose of insulin on Day 1 was 1.2unit/kg/day in IV group and 1 unit/kg/day in SC cohort.

Discussion: Sub-cutaneous administration of insulin is effective and cheap in management of paediatric DKA. Earlier reports used a cut-off of a pH>7 to use SC insulin therapy in DKA. This study has established that pH is not a limiting factor for treatment of DKA in non-ICU setting.

Conclusion: SC insulin can be a cost effective alternative in treatment of DKA in resource-poor countries.

P1-313

Familial versus non-familial type-2 diabetes mellitus in children and adolescents: Clinical and Biochemical Data

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Familial clustering of type-2 diabetes is well-known. In adults, the prevalence of diabetes is higher among patients with diabetic parents. The Framingham offspring study found that maternal and paternal diabetes conferred equal risk for offspring type-2 diabetes.

Objectives: We conducted this study to compare the clinical characteristics of children and adolescents with family history of type- 2 diabetes mellitus, in one or both parents, (FT2DM) with those without a family history of DM (NFT2DM).

Patients and Methods: This was a cross-sectional descriptive study to determine the clinical presentation and prevalence of beta cell autoimmunity (Anti GAD, anti-islet cell and anti-insulin antibodies), thyroid function (Free thyroxine (FT4) and TSH) and anti-thyroid peroxidase antibody (ATPO) and anti-tissue trans-glutaminase (ATT) in a randomly selected cohort of children and adolescent (< 16 years) with FT2DM (n= 13) and compare them with those for children without family history of DM (NFT2DM (n = 26) at their first presentation at Hamad General Hospital Diabetes Center, Doha, Qatar

Conclusion: In this study, FT2DM occurred more in males than females, after 10 years of age, and all presented with hyperglycemia without ketosis. Clinical and subclinical hypothyroidism occurred more in the NFT2DM and they had a higher prevalence of hypercholesterolemia and triglyceridemia.

Familial Diabetes	NFT2DM	FMT2DM
Prevalence of beta-cell autoimmunity		
Anti-GAD	29.3%*	0%
Islet cell AB	29.4 %	42.85 %*
Insulin AB	58.3 %	50 %
Anti-GAD +ICA2	8.3 %	0%
Prevalence of thyroid disorder		
1-T4 (<11)	11.5 %*	0%
2-TSH (5.6-10)	8%	8.3 %
3-TSH (>10)	6 %	8.3 %
4-TPO (>100)	34.6%	30%
5-TPO (>100)+ NL TFT	23.1%	20%
6-TPO (>100)+ hypothyroid (T4 <11) or TSH >10)	7.7%*	0%
7-TPO (>100)+ subclinical (TSH 5.6-10)	3.8 %*	0%
1-ATT IgA>10	8.7 %*	0%
2-ATT IgG >10	0%	0%
1-PH <7.3	2.63%*	0%
2-Hco3 <15	2.6.%*	0%
5-ketosis	34.2%*	0%
Gender		
1-Female	58.9%*	38.46%
2-Male	39.2%	61.54 %*
Age years		
0 to 4	0%	0%
5 to 9	24.14%*	0%
10 to 14	75.68%	100%*
LFT		
1. high ALT	46.34%	46.2%
2. high AST	24.39%*	7.69%
3. high ALP	12.8%	7.69%
Lipid profile		
High LDL	10.26 %	0%
Low HDL (low)	43.589%	55.5%
High Cholesterol	5.13%*	0%
High Triglycerides	17.9 %*	10%

P1-314

Comparison between patients and families who routinely download data and those who do not download data at home in the management of Type 1 diabetes

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Background: In type 1 diabetes (T1D), optimal glycaemic control requires intensive self-management to reduce the risk of complications. While routine downloading and review of blood glucose data is part of clinical practice of healthcare providers in an outpatient setting, patients and families are also educated, advised and encouraged to regularly download and review blood glucose data at home in order to make adjustments to insulin dosing for carbohydrate intake and insulin sensitivity factors. In this study, we describe the characteristics between two groups of patients with T1D who routinely download and review their blood glucose data at home compared with a cohort of patients who do not download data at home.

Methods: Patients and their families were considered as “routine downloaders” (RD) if their blood glucose device data was downloaded and reviewed at home at least once a month between routine clinic visits which was scheduled every three months. “Non-downloaders” (ND) were defined by those who did not download or review data at home at least once a month, despite being educated on the use of free software and encouraged by healthcare professionals to download. We evaluated demographics, age, duration of diagnosis, socioeconomic deprivation scores, quality of life scores and mean Hb1A1c between RD and ND patients.

Results: 98 patients were included in the study (52 males) with a mean age at diagnosis of 7.4 years ($SD \pm 3.8$, range 1.1–15.0), mean diabetes duration of 5.2 years ($SD \pm 0.36$). The patients’ characteristics are reported in Table 1 with 33 patients in the RD group and 65 patients in the ND group. Mean HbA1c (mmol/mol) in the preceding 12 months was significantly better in the RD group compared to ND group (60 vs 66, $p=0.03$). The ND group had significantly poorer overall deprivation scores, poorer employment and education levels ($p<0.05$ in all domains). Multivariable logistic regression analysis examining the factors affecting families downloading at home found that overall deprivation was the only independent determinant ($p=0.03$).

Conclusion: This study shows that social deprivation is an important determinant towards the practice of routinely downloading data at home for families and children with T1D. Healthcare professionals should target deprived areas with further support, education and resources for management of T1D.

P1-315**Immune Status in Children and Adolescents with Type 1 Diabetes***Irina Osokina*

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Introduction: There are the inconsistent data about a role cellular and humoral immunity in pathogenesis of type 1 diabetes mellitus.

The aim: of this research was to study features of the immune status and of the activity of metabolic enzymes in lymphocytes of blood in children with type 1 diabetes.

Methods: Cellular and humoral immunity parameters were studied in 94 patients with type 1 diabetes mellitus aged 6–18 years (the mean age was 11.6 ± 0.3 yrs) and 104 controls the same age. The patients were divided into 3 groups with different duration of diabetes: up to 1 year, 1–5 years, and more than 5 years. The metabolic control of diabetes we estimated on levels of HbA1c. Population and subpopulation composition of peripheral blood lymphocytes was studied by method indirect immunofluorescence. Serum concentrations of the main immunoglobulin classes were measured by radial immune diffusion. The activity of NAD - dependent dehydrogenases investigated by the bioluminescence method.

Results: 88% of the diabetes patients had HbA1c levels higher than 7.5%. The average HbA1c was 8.9%. At the initial stage of diabetes the immunoreactivity status in children and adolescents manifested by depression of T-cellular component of the immune system and activation of humoral immunity, this depression progressing with the disease duration. The concentration CD16+ cells was increased in all patients, irrespective of diabetes duration. The content of HLA-DR+ lymphocytes was increased at the stage of initial diabetes and decreased to the norm later. No definite patterns in changes of serum immunoglobulins A and M concentrations could be distinguished during the observed period of disease.

Conclusion: This study has shown, that there are the suppression of T-cellular immunity and the activation of humoral immunity in the initial stage of type 1 diabetes.

P1-316**An evaluation of the accuracy of a flash glucose monitoring system in children with diabetes in comparison with venous blood glucose**

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Aims: To evaluate the performance of a factory-calibrated flash glucose monitoring system in children with diabetes compared to venous blood glucose (BG).

Methods: A total of 13 hospitalized participants newly diagnosed with type 1 diabetes, aged 1~14 years old, were involved in

the study. Sensor glucose measurements on days 2, 3, 6, 7, 12 and 13 of wear were compared with venous BG. During these days, the venous BG results were obtained either 4 or 7 times per day.

Results: The accuracy was evaluated against venous BG, with 469 of 469 (100.0%) sensor and venous BG pairs within consensus error grid zones A and B, including 94.7% in zone A. The overall mean absolute relative difference (MARD) was 11.67%. The MARD of blood glucose lower than 4.0 mmol/L (MARD=16.89%) was higher than blood glucose between 4 to 10 mmol/L (MARD=11.58%) and blood glucose higher than 10 mmol/L (MARD=7.79%). Compared to venous BG, the MARDs of wear days 2, 3, 6, 7, 12 and 13 were 11.53%, 9.66%, 11.79%, 10.89%, 13.18% and 13.92%, respectively, with no statistically significant difference ($P=0.25$). The median ARD was highest when the glucose decreased >0.11 mmol/L/min (20.27%), and lower than 10.00% when the glucose changing between 0.06 and 0.11 mmol/L/min, changing <0.06 mmol/L/min and increasing >0.11 mmol/L/min.

Conclusions: The accuracy of the system is good and remains stable over 14 days of wear; however, the accuracy depends on the glucose level and rates of glucose concentration changes.

P1-317**Unexplained neonatal deaths among Kurdish consanguineous families: Importance of recognizing congenital hyperinsulinism and testing for K_{ATP} channel gene variants**

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Context: Neonatal hypoglycemia due to congenital hyperinsulinism (CHI) is a potentially life-threatening condition. Severe forms of CHI, caused by autosomal recessive variants in K_{ATP} channel subunit genes (*ABCC8*, *KCNJ11*), are more prevalent in regions with high consanguinity. These regions also have a high neonatal mortality rate with many deaths remaining unexplained.

Patients and Methods: We analyzed three patients with CHI born into three separate Kurdish consanguineous families (two families had a combined history of four unexplained neonatal deaths with seizures).

(1) A one year old girl presented at six days of life with recurrent convulsions due to hypoglycemia (blood sugar 2.05 mmol/l, insulin 58 mIU/l, C-peptide 2242 pmol/l).

(2) A four year old girl with a severe developmental delay had recurrent symptomatic hypoglycemia from four days of age which was only treated with frequent feeding and starch. At three years, CHI was confirmed (blood sugar 2.78mmol/l, insulin 8.1mIU/l, C-peptide 2300pmol/l).

(3) A one year old girl presented at three weeks of age with convulsions and loss of consciousness due to blood glucose 2.5mmol/l (insulin 14.6 mIU/l, C-peptide 1580 pmol/l).

DNA was extracted from blood of the patients', their parents' and unaffected siblings'. ABCC8 and KCNJ11 genes were tested in the patients by Sanger sequencing. If potential variants were not published in the HGMD database, their pathogenicity was evaluated by their absence in the ExAC database, by predictions of in-silico programs and the American College of Medical Genetics (ACMG) standards. Thereafter, selected variants were confirmed in family members.

Results: In each of the three patients, novel pathogenic homozygous variants were found. All have heterozygous healthy parents and unaffected siblings who tested negative or heterozygous.

Patient (1) has variant p.Met1Val in KCNJ11, patient (2) has variant p. Trp514Ter in ABCC8, and patient (3) has variant p. Tyr26Ter in KCNJ11. Variants (2) and (3) cause a stop signal leading to premature protein termination.

In addition, all three variants were classified as pathogenic by all tools described above.

Conclusion: CHI caused by K_{ATP} channel variants was elucidated in three children, providing a highly probable explanation for their siblings who died as neonates. In regions with high consanguinity, a small but significant percentage of all unexplained neonatal deaths could be due to CHI. Future lives could be saved by the timely diagnosis of CHI when encountering a neonate with unexplained seizures or other signs of recurrent and/or persistent hypoglycemia.

P1-318

Improving The Transition to Adult Care for Adolescents with Type 1 Diabetes: Effect of Transition Readiness, Self-Efficacy And Diabetes Distress on Glycemic Control During Transition

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Aim: The transition from pediatric to adult care is characterized by inadequate medical follow-up, poor self-management, and higher risk for adverse outcomes. We aimed to determine whether self-efficacy, transition readiness or diabetes distress are associated with glycemic control (HbA1c) among adolescents with T1D during the transition period.

Methods: Cross-sectional study of adolescents (ages 17 years) with T1D followed at the Montreal Children's Hospital diabetes clinic. Adolescents were recruited during the year prior to transfer to adult care and completed validated questionnaires on self-efficacy, transition readiness (TRAC) and diabetes distress (T1-DDS). **Primary outcome:** mean HbA1c (%) during the year prior to transfer. To analyse the association between our exposures and HbA1c, we used Pearson correlation and Chi Square test.

Results: We recruited 74 adolescents with T1D (29 male, 39.2%). Mean age (\pm SD) at diagnosis was 9.1 (\pm 4.0) years and age

at transition (last pediatric diabetes visit) was 17.9 (\pm 0.2) years. Mean diabetes duration was 8.5 (\pm 4.0) years. Mean HbA1c was 8.88% (\pm 1.33%). Six adolescents (8.1%) had HbA1c \leq 7.5%, 39 (52.7%) between >7.5- <9.0 % and 29 (39.2%) \geq 9.0 %. Twenty-eight adolescents (37.8%) had TRAC scores \geq 8, indicating transition readiness and 10 (13.5%) had T1-DDS total scores \geq 3, indicating diabetes distress. Transition readiness was associated with lower HbA1c (r =-0.34, p =0.003). Amongst those with poor glycemic control (HbA1c >9.0), 50% were not ready for transition compared with 21% deemed ready for transition (p =0.015). 80% of adolescents with diabetes distress had poor glycemic control compared with 33% without diabetes distress (p =0.004). Higher self-efficacy scores were associated with lower HbA1c (r =-0.29, p =0.012).

Conclusion: Efforts to improve healthcare transition should focus on improving self-efficacy and transition readiness while addressing diabetes distress so as to support adolescents in developing their autonomy and in preparing them for an adult model of care.

P1-319

Gene dosage changes in the GCK gene not detected by Sanger DNA sequencing in two patients with phenotypic MODY 2

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Background: Maturity onset diabetes of the young 2 (MODY 2) is phenotypically characterized by elevated fasting and post-prandial blood glucose (BG) levels and no diabetes auto-antibodies. Inheritance is autosomal dominant, and it is caused by variants in the glucokinase (GCK) gene with resetting of the pancreatic glucose sensor to a higher level. It is essential to detect MODY 2 patients as they do not require treatment.

Objective and Hypothesis: The objective of the study was to present two phenotypic MODY 2 patients with gene dosage changes in the GCK gene, not detected by Sanger sequencing.

Methods: Two patients with phenotypic MODY 2 were included. Genetic methods: Sanger DNA sequencing and Multiplex ligation-dependent probe amplification dosage assay (MLPA).

Results: Patient one was a slim boy referred for diabetes mellitus (DM) 7.5 yr., with two fasting BG of 7.0 and 8.0 mmol/L, respectively, and a haemoglobin A1c (HbA1c) of 47 mmol/mol (6.4 %). His parents were non consanguineous. The father and grandfather had type 2 DM. BG profiles showed BG of 6.5 – 10 mmol/L. The boy tested negative for GAD65 and IA2 antibodies. Sequencing of all GCK exons did not reveal any gene variations, but MLPA detected a heterozygous whole GCK gene deletion, which could not be demonstrated in his parents, indicating that the deletion was a de novo variant. Patient two was a slim girl referred for DM 9.7 yr., with two HbA1c of 49 mmol/mol (6.6 %) and 48 mmol/L (6.5 %), respectively. Her parents were non consanguineous and no family members had DM. BG profiles

showed BG of 6.1 - 9.3 mmol/L. The girl tested negative for GAD65, IA2 and Zink Transporter 8 antibodies. Sequencing of all GCK exons did not reveal any gene variants, but MLPA detected a heterozygous duplication of exon 2 and 3. The father, but not the mother, was carrier of the same duplication in the GCK gene, and his HbA_{1c} was 43 mmol/mol (6.1%). The gene variant of patient 2 has not previously been reported in the human genome database.

Conclusion: These cases emphasize the importance of gene dosage analysis by MLPA in patients suspected for a GCK variant, when no variant is identified by direct sequencing. Detection of a GCK variant has implications for the patient as well as for family members carrying the same gene variant, as MODY 2 patients generally do not need treatment.

P1-320

Assessment of Vascular Endothelial Dysfunction Using Brachial Artery Flow Mediated Dilatation and Carotid Intima Media Thickness in Children and Adolescents with Type 1 Diabetes

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with diabetes. Macro- and micro-vascular complications are involved in the pathophysiology of CVD and the increased risk of developing atherosclerosis in this population. A probable association between type 1 diabetes (Type 1 D) and CVD has been attributed to chronic uncontrolled hyperglycemia, inflammation, endothelial dysfunction (ED), and subclinical manifestations of vascular disease. This study aimed at assessing the endothelial function in children and adolescents with Type 1 diabetes (T1DM) using flow-mediated dilatation (FMD) response and carotid artery intima-media thickness (cIMT) as indices of presence of subclinical atherosclerosis. A cross sectional study included 100 children and adolescents with T1D with age range from 5 to 15 years and disease duration more than 5 years, following in Diabetes Unit, Children's Hospital, Cairo University. Fifty age and sex matched controls were also included. Patients on any medications other than insulin, especially antihypertensive, antiplatelet or lipid lowering medications were excluded. Also Patients with anemia, family history of hypercholesterolemia or premature cardiovascular disease were excluded. Glycated hemoglobin, urinary albumin/creatinine ratio, and fasting lipid profile were studied. FMD and cIMT were assessed with high-resolution ultrasound using standardized measurements.

This results showed that FMD was significantly lower in patients in the T1D Group ($2.9 \pm 1.9\%$) compared with controls ($8.5 \pm 1.1\%$; P-value < 0.001). Similarly, cIMT differed significantly between T1D patients (0.48 ± 0.06 mm) and controls (0.46 ± 0.07 mm; P-value = 0.02). There was significant positive correlation between cIMT and duration of diabetes ($r=0.6$, $p<0.001$), age of onset of diabetes ($r = 0.3$, $p=0.001$), mean HbA_{1c} ($r=0.6$, $p < 0.001$), LDL cholesterol ($r=0.6$, $p < 0.001$) and significant negative correlation with HDL cholesterol levels ($r=-0.6$, $p < 0.001$).

On the other hand, there was significant negative correlation between FMD% and duration of diabetes ($r= -0.2$, $p=0.004$), total insulin dose ($r= -0.2$, $p= 0.01$), mean HbA_{1c} ($r= -0.37$ $p < 0.001$), total cholesterol ($r= -0.2$, $p = 0.009$), LDL cholesterol ($r= -0.3$, $p=0.002$), serum Triglycerides ($r= -0.4$, $p=0.001$) and significant positive correlation with HDL cholesterol ($r =0.3$, $p= 0.001$).

Diabetic patients had statistically significant higher cIMT and lower FMD than normal healthy controls which reflects the significant presence of higher risk of endothelial dysfunction, premature atherosclerosis and peripheral vascular disease in this type of population. The role of T1D in atherosclerosis is still poorly understood and further large-scale studies are still needed.

P1-321

A Case of Late-Onset Monogenic Diabetes Due to a Homozygous Variant in the GCK Gene

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Introduction: Heterozygous loss-of-function mutations in the glucokinase (GCK) gene cause MODY 2. Conversely, homozygous loss-of-function mutations in the same gene give rise to permanent neonatal diabetes mellitus (DM). Previously, two patients diagnosed with DM in adolescence and had homozygous GCK mutations were reported. Variants in these patients have been shown to exhibit inactivated kinetics that are indistinguishable from neonatal onset mutations, but exhibit thermostability properties, which alleviate disease severity.

Aim: To present genotypic and phenotypic features of a patient diagnosed with DM at the age of 3 years due to a homozygous variant in the GCK gene.

Case: We examined medical records of a 13-year-old male with DM, who had good metabolic control (HbA_{1c} 6-7%) under treatment with a single daily dose (0.2 units/kg) of insulin glargin and no ketoacidosis attacks since diagnosis. He was diagnosed with DM at the age of three years with the complaints of polyuria and polydipsia. At the time of diagnosis, he had a fasting venous glucose, 172mg/dL with no ketonuria and acidosis; C-peptide, 1.1 ng / mL (N, 0.9-7.1); insulin, <2 mIU / mL (N, 1.9-23); HbA_{1c}, 7% (N, 4-6); and negative diabetes auto-antibodies. His parents were first degree cousins. There was no history of DM in the family except the grandmother with type 2 DM. On examination; weight was +0.18 SDS, height +0.74 SDS, puberty Tanner stage II and other physical examinations were normal. Owing to the inappropriate low dose insulin requirement beyond honeymoon period and negative diabetes auto-antibodies that are not compatible with type 1 DM, a next generation sequencing of MODY genes (GCK, HNF1A, HNF1B ve HNF4A genes), which revealed a novel homozygous variant c.1222 G>T in GCK gene was identified. His mother and father had same heterozygous variant in the GCK gene and were diagnosed with MODY 2 (mild fasting hyperglycemia and elevated HbA_{1c}) after genetic counselling.

Conclusion: In GCK mutations, the homozygous and heterozygous status of the variant, as well as protein instability and thermostability properties may also contribute to the genotype-phenotype correlation. Despite the homozygous mutation in our patient, he had late-onset and mild disease, which can be related to the thermostability of GCK protein. Molecular genetic analysis of MODY genes in patients, whose clinical and laboratory findings do not match with type 1 DM can define novel mutations and provide a better understanding of the genotype-phenotype correlation in MODY.

P1-322

Neonatal diabetes and Glis3 mutation: a new phenotype

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Background: The transcription factor Gli-similar 3 (Glis3) is predominantly expressed in the pancreas and it has a critical role in the development of insulin producing β-cells, thyroid and kidney. Mutations in GLIS3 is a rare cause of neonatal diabetes associated with congenital hypothyroidism, congenital glaucoma and polycystic kidney. We report a new case from consanguineous parents with homozygous novel mutation in GLIS3 gene.

Case Presentation: our patient is a male child, who was born with a weight of 1900g, length of 44 cm and head circumference of 44 cm after 39 weeks of gestation. He was hospitalized at the age of 15 days for weight loss without digestive disorder or dietary error. His weight was 1800g (below the third percentile). The biological analysis revealed hyperglycemia (blood glucose: 35 mmol/l) associated with glucosuria without ketonuria requiring continuous intravenous insulin (0.05 IU/kg/h) and was subsequently treated with subcutaneous insulin (Actrapid® then a mixture of Actrapid® and Insulatard®, two injection regimen). He had a high level of insulinemia (44.8 mU/l) and a low level of C peptide (0.43 µg/l). Ultrasonography and CT scan revealed normal appearance of the pancreas. At the 25th day of life, he developed macroglossia and edema. Thyroid assessment showed free thyroxine (FT4) of 1.2 pmol/l (normal: 12–22) and serum TSH of 46 µIU/l (normal: 0.27–4.5), which required a treatment with L-thyroxine (10mcg/kg/d). Anti-thyroglobulin and anti-microsome antibodies were negative. Thyroid ultrasound showed normal thyroid lobes, and the scintigraphy did not show any fixation. After 5 months of follow-up, he developed dysmorphic syndrome (bulging forehead, micrognathia and badly hemmed ears), convergent strabismus, glaucoma, bilateral perception deafness, epilepsy with psychomotor retardation. Liver assessment did not show cholestasis and renal echography did not show renal cysts. Target blood glucose have been difficult to achieve due to labile glucose level. Glycosylated haemoglobin was between 8 and 12%. Genetic assessment revealed homozygous stop mutation GLIS3: C1597c A / p S 295x with new phenotype.

Conclusion: this case is characterized by the absence of renal and hepatic involvement and a particular clinical phenotype with psychomotor retardation and epilepsy.

P1-323

Diabetes type 2 in non-obese neurologically impaired children and adolescents: a new emerging entity?

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Background: Insulin resistance (IR) plays a key role in the pathogenesis of type 2 diabetes (T2D). In neurologically impaired (NI) children unfavorable cardio-metabolic risk profile with high prevalence of IR has been reported. We evaluated the prevalence of T2D in NI children and adolescents, in order to define if a dedicated glucose monitoring may be recommended in these subjects.

Patients and Methods: We retrospectively evaluated 63 patients (11.4 ± 4.0) with severe disabilities. Auxological parameters were recorded. Metabolic blood assays included fasting blood glucose (FBG), fasting insulin, triglycerides (TG). IR was detected with the homeostasis model assessment for insulin resistance (HOMA-IR > 97.5th percentile for age and sex) and triglyceride-glucose index (TyG index > 7.88). Elevated FBG was defined with values > 100 mg/dl. T2D was defined according to ADA criteria.

Results: ISI, pathological TyG index and elevated FBG were observed respectively in 41.3%, 63.5% and 11.1% patients. No significant correlation between HOMA-IR and TyG was found ($r = 0.17$ $p = 0.20$). T2D was diagnosed in 2/63 patients (3.2%; 1 male and female) at the age of 4 and 8 years respectively. Both patients were asymptomatic and diabetes was incidentally detected during a routine checkup. Clinical and biochemical data and treatment following diagnosis was reported in table 2. In both patients, IR or surrogate markers of IR were detected. The prevalence of diabetes was higher in prepubertal compared to pubertal subjects ($p = 0.03$), similarly in males and females ($p = 0.8$).

Conclusions: T2D in NI children and adolescents could represent a new emerging entity in subjects without obesity. Insulin resistance and/or surrogate marker of insulin resistance index may be useful for the early screening of these at-risk disabled populations

P1-324

Cataract in type 1 diabetes mellitus patients- a nationwide population-based study

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Though most ophthalmologic emphasis has been stressed on the influence of retinopathy on the young diabetic community, lesser known is the complication of cataract, which has resulted

in more than half of the blindness worldwide. This study attempts to stratify the epidemiology and risk factors of cataract in the type 1 diabetes mellitus (T1DM) population using data extracted from the National Health Insurance Research Database (NHIRD) in Taiwan.

A two-step study was conducted. For matching on age and gender with the Longitudinal Health Insurance Database (L HID), a total of 3,622 T1DM cases who registered as catastrophic illness patients in Registry between 1998 and 2007 were included for evaluation of epidemiology. For identifying risk factors of cataract in T1DM population, a total of 9,032 T1DM cases who registered between 1998 and 2013 were enrolled, excluding those with pre-T1DM cataract.

Compared to L HID, the hazard ratio (HR) of cataract in T1DM population was 5.81 (95% CI 4.60-7.33) with a higher gender-specific HR in females (6.29, 95% CI 4.63-8.55). In T1DM population, peak incidence of cataract is reached in the 20 to 29 age group compared to the 60+ age group in the L HID population. In the second step of the analysis, half of the eligible T1DM patients were diagnosed before the age of 20 (50.1% in total 9032 patients). The overall incidence of cataract in T1DM group was 9.1% with a higher gender-specific incidence in females (10.4% vs. 7.7%, p < 0.001). T1DM patients with cataract were found to be at a higher rate of accompanying medical conditions, including retinopathy, glaucoma, amputation, and end-stage renal disease than those without cataract (all p < 0.001).

Cataract seemed to be not only more rampant but also more premature in T1DM patients, especially those of female gender. T1DM patients with cataract presented with higher rates of DM-associated complications which might suggest poor glycemic control to be a predisposing factor.

one of A/G heterozygous type was 50%. The study on distribution of CTLA4 gene polymorphism among the patients with the hereditary burden of diabetes mellitus demonstrated that the frequencies of A and G alleles in the control group were 38.6% and 61.4%, respectively. The frequencies of A/A and G/G homozygous genotypes were 4.5% and 27.3%, respectively, the one of A/G heterozygous type was 68.2%. The association of G allele and heterozygous genotype of CTLA4 gene A49G polymorphism registered in the children of patients with type 1 diabetes mellitus and their blood relatives could be implicated in diabetes mellitus risk and used as a marker in the development of a complex for early diagnosis of the disease.

P1-326

Copy Number Variation (CNV) Sequencing Identifies a Novel Mutation of the Glucokinase Gene in Maturity-onset Diabetes of the Young

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Background: Maturity-onset diabetes of the young (MODY) is a cluster of early-onset, monogenic disorders which is inherited in autosomal dominant form. It is mainly caused by genetic defects in beta-cell, which results in beta-cell dysfunction. Till now, 14 MODY types specified by mutation in respective 14 genes with their etiologies are known. Among them, glucokinase (GCK) gene encodes glucokinase enzyme which plays a crucial role in the regulation of insulin secretion.

Methods: Clinical features and laboratory data were collected from the patient and her family member 10, and linkage analysis and copy number variation (CNV) detection were performed to screen the mutation of all the 14 MODY gene.

Results: The 3-year-old patient was referred to the endocrinology clinic for evaluation of elevated fasting blood glucose (FBG) measurements. Family studies and laboratory review of other families of hers conformed to the clinical features of MODY. Genetic testing showed the autosomal dominant, deletion mutation in the GCK gene, which is correlated with GCK-MODY. Of the candidate CNV regions, one copy deleted respectively in exon 8, exon 9, exon 10 and exon 11 in all the patients of this family, while normal people have no such deletion mutation, which is a novel mutation of GCK gene.

Conclusion: MODY represents a combination of genetic, metabolic, and clinical heterogeneity. MODY has several subtypes depending upon the involvement of genes and their mutations. Our patients likely represented a novel deletion mutation of GCK-MODY. Besides linkage analysis and exon mutation screening, CNV sequencing might be used to identify other novel GCK mutations.

P1-325

Association of CTLA-4 gene with the familial diabetes mellitus

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The work was initiated to study role of CTLA4 gene in the onset of familial diabetes mellitus. The samples of peripheral blood taken from children (mean age 12.5 years) of patients with type 1 diabetes mellitus and their blood relatives, such as parents and siblings, and apparently healthy subjects were used in the study. Among the recruits, there were 56.5% of boys and 43.5% of girls. The findings from the genotyping of CTLA4 gene 49A/G polymorphism demonstrated no significant deviations of the genotypes observed from the expected ones in the group of apparently healthy subjects and the diabetics.

The frequencies of A and G alleles in the control group were 57.7% and 42.6%, respectively. The frequencies of A/A and G/G homozygous genotypes were 32.7% and 17.3%, respectively, the

The Paediatric Diabetes Service in England and Wales – Learning from Sweden’s Improvement Journey

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A gradual reduction of national median HbA1c levels in England and Wales since 2009 can be attributed to development of a network approach to care supported by the National Paediatric Diabetes Audit (NPDA) and a Best Practice Tariff in England, introduced by the Department of Health in 2012. This delivery of a co-ordinated national programme of support for 173 multi-disciplinary teams distributed across over 140 NHS Trusts and Health Boards, has been at risk of plateauing in recent years. To maintain the momentum towards achieving improvements comparable to international results, a new way to engage teams and their host organisations was required.

Evidence from Sweden, which has reduced its HbA1c levels markedly in recent years, demonstrates the impact that a programme of Quality Improvement can have on stimulating units to improve outcomes. In 2017, a Quality Improvement Collaborative model was developed in partnership with colleagues from Linkoping University Hospital in Sweden. 16 teams applied to participate in a pilot Quality Improvement Collaborative with ten ultimately chosen to begin a 9-month programme of training from November 2017. All members of the 10 successful MDTs were expected to attend the programme of training together; comprising 2 residential weekends and 2 one-day events, lunchtime webinars for team champions and access to a secure online platform to share resources and ideas between events.

The ethos of the programme was to provide teams with the QI methodology to identify, design and analyse their own interventions specific to their teams and to the needs of the children and young people and their families that they care for. Each of the 10 teams highlighted very individual areas of focus ranging from the newly-diagnosed patient pathway, self-management resources in the community, Diasend download education and access, support for patients on pumps and the outpatient clinic experience.

Initial run-chart data has shown up to 10% reduction in mean and median HbA1c post-pilot. As part of the new National Children and Young People’s Diabetes Quality Programme that includes annual self-assessment and a peer review process, the pilot Quality Improvement Collaborative model has now been adapted for rollout to over 100 units across England and Wales. It is our hope that this will be the stimulus to drive sustainable development of paediatric diabetes services in England and Wales and help bring transformative improvements to the care of children and young people with diabetes and their families in the future.

Creating a neural network model based on glycemic variability indices to predict the degree of compensation for type 1 diabetes

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Actuality: Standard methods for determining the compensation of the disease don’t always reliably reflect the level of the glycemic control of the patient, which leads to decompensation diabetes and reduce the quality and duration of life for patients. Evaluation of glycemic variability indices allows the physicians to predict the risk of developing life-threatening conditions and compensate the diabetes

Aim: To conduct a comparative analysis of glycated hemoglobin (HbA1c) and glycemic variability indexes to predict the degree of compensation for the diabetes mellitus type 1

Materials and Methods: The study included 80 patients with diabetes mellitus type 1 with insulin pump therapy with the possibility of Continuous Glucose Monitoring System (CGMS). All patients done analysis of HbA1c and transmitted data to the doctor for recommendations. As independent parameters for predicting the HbA1c, we chose the glycemic indexes calculated by using the EasyGV: standard deviation, long-term glycemic index, lability index, hypoglycemia and hyperglycemia risk index, M-value. The regression neural network model was built in the environment of statistical computing type R using the software package Neural Network Wizard 1.7 (BaseGroup Labs, Russia). Statistical analysis was performed using SPSS 23.0 (IBM SPSS Statistics, USA). Descriptive statistics for abnormally distributed quantitative parameters are represented by the median and 25; 75 percentiles Me [Q1; Q3]. Statistical significance of differences was assessed by the Mann-Whitney U-test. Differences were considered significant at $p < 0.05$.

Results: There was a significant improvement glycemic variability indexes by the end of the study. The optimal model was based on a multilayer perceptron with three hidden layers and the number of neurons in each layer. The constructed model showed a very high value of the coefficient of determination $R^2 = 0.987$, which indicates a high confidence in predicting the level of HbA1c. When creating a traditional model based on multiple regression, the coefficient of determination was $R^2 = 0.254$, which indicates a low prediction accuracy of the HbA1c level and a higher residual error.

Conclusions: The neural network model with a high index of determination based on glycemic variability indexes demonstrates a significantly higher accuracy in predicting the level of HbA1c in diabetes patients, which makes it possible to assess the degree of compensation for the disease and provide a personalized approach in treating these patients

P1-329

Evaluation of AGP reports in patients with type 1 diabetes using intermittently viewed continuous glucose measurement system (iCGM)

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Introduction: Reduction in glycemic variability and HbA1c levels are achieved by the use of continuous glucose measurement systems (CGM) in the patient with Type 1 diabetes mellitus (T1DM). Intermittently viewed CGM (iCGM) using flash technology have been used increasingly by diabetics and their families because of practicality. Evaluating of ambulatory glucose profiles (AGP) is very important in the management of T1DM.

Aim and Methods: In order to investigate the effectiveness of iCGM in the management of T1DM, AGP reports were evaluated in this study. The results of 80 CGM reports of 52 patients with T1DM were analyzed. Of those, 70 iCGM AGP reports were evaluated and reviewed in detail.

Results: The median age was 9.9 years (2.3-19 years) in 52 cases (20 male, 32 female). Twenty-five (48.1%) of the patients used insulin pumps, and others were on multiple doses of insulin injection therapy. A1c values were $7.81\% \pm 0.85$ in insulin pump users and $7.63\% \pm 1.04$ in multiple doses insulin injection ($p = 0.496$). Sensor types were freestyle libre in 42 cases, guardian connect in 2 cases, dexcom g4 in 1 case, and 640G model insulin pump in 7 cases. When evaluating AGP reports; digital A1c was $8.17\% \pm 1.28$, whereas serum A1c was $7.81\% \pm 1.02$ ($p < 0.05$) in 70 reports of 42 patient for freestyle libre. Digital A1c was 7.62 ± 0.54 , whereas serum A1c was 7.57 ± 0.78 ($p < 0.05$) for 640G system. Due to small number of 640G pump users, A1c levels were not compared with the freestyle libre. Freestyle libre AGP report showed that mean time in range of 41.8%, time in hyperglycemia of 51.9%, and time in hypoglycemia of 6.3%. There was no difference in target range, time in hyperglycemia and time in hypoglycemia between the pump users and others.

Discussion: The study showed that A1c value in AGP report was correlated with the serum A1c level. Using insulin pump did not show improvement in A1c and time in range in target. It shows that freestyle libre users who were not using insulin pump may be paying more attention for diabetes care. According to the results, the use of iCGM affects the management of diabetes positively.

P1-330

Evaluation of Clinical, Laboratory and Therapeutic Features and Long Term Follow-up Results in 44 Cases with Genetic Diagnosis of MODY; Single Center Experience

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Introduction-Aim: MODY;It is an autosomal dominant, rare type of diabetes that occurs in young people as a result of mutations of beta cell function and genes involved in insulin secretion. The cases may be misdiagnosed as Type1 and Type2 diabetes. Considering that MODY is clinically and genetically heterogeneous, the findings should be evaluated correctly. It is important to define the clinical-laboratory characteristics of diagnosis and follow-up of patients diagnosed genetically as MODY. The aim of this study was to investigate the clinical and laboratory features of patients with MODY and to investigate the relationship between genotype and phenotype.

Methods: A total of 44MODY cases were included in the study. Mutations in HNF4A, GCK, HNF1A, PDX1, HNF1B, NEUROD1, KLF11, CEL, PAX4, INS and BLK genes were studied by Sanger sequence and targeted next-generation sequencing analysis method. The cases who were treated according to the MODY type and the follow-up data and were followed up for at least 3 years were included. Anthropometry, examination, blood glucose and HbA1C levels were evaluated at3-month intervals.

Results: The age of diagnosis of 44 patients with MODY (24 male) was 9.4 ± 4.7 (1-17) years. Except for three cases, the height and weight were normal. 55% of the patients were diagnosed as random hyperglycemia, 36% with symptomatic hyperglycemia and 9% with ketosis. All cases had a family history of diabetes. Blood glucose levels (97-664mg/dl), HbA1C (5.2-15.6%) and C-peptide levels (0.2-5.9ng/ml) were quite wide in the diagnosis. Only 2 of 44 cases had anti-GAD positivity and anti-insulin and islet-cell-antibodies were negative in all cases. The most common mutation was found in 55%GCK gene (5 new mutations) while the other distribution was; KLF11-MODY (n=7;16%), HNF1A-MODY (n=6;13%), NEUROD1-MODY(n=2), HNF4A-MODY (n=2), PDX1-MODY, CEL-MODY (new mutation) and HNF1B-MODY mutation were detected in one case. All cases of GCK, NEUROD1, PDX1 and CEL-MODY were treated only with diet, HNF1A-MODY sulfanylurea treatment, 1 of metformin in KLF11-MODY, 5 cases with intensive insulin, HNF4A and HNF1B-MODY.

Conclusion: In this study, it was found that the association with the presence of hyperglycemia, the presence of 2-3 generations of diabetes in the family, anti-insulin and islet cell antibody negativity findings were strongly differentiated for MODY. Blood glucose levels, HbA1C and C-peptide levels were found to be in a wide spectrum according to genetic heterogeneity. The most common GCK mutation was 55% of all cases. The cases with GCK, NEUROD1, PDX1 and CEL-MODY only with dietary

treatment and HNF1A-MODY cases with sulfanilurea treatment, were found to be in good metabolic control during long-term follow-up. In other MODY types, it was observed that they needed intense insulin according to beta cell reserve.

Keywords: GCK, HNF1A, KLF11, MODY

P1-331

Design and Implementation of an Integral System of Clinical Follow-Up and Glucose Monitoring in Children Affected of Type 1 Diabetes, in Andalusia

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Introduction: The incorporation of the interstitial glucose monitoring system, in the offer of services in the Andalusian Public Health System (APHS), means an opportunity for the implementation of a model of integration, and follow-up of glucose data, and the evaluation of their impact in health results.

Purpose (Aim): The design and implantation of a model that allows the identification, registration of clinical data, integration of interstitial glucose data and valuation of the results in health, in the pediatric population affected of type 1 diabetes, and user of flash monitoring systems in the APHS.

Methods: The target population (type 1 diabetes and age from 4 to 18) was estimated in 3000 patients. Thirty three hospitals, 50 endocrinology hospital services, and 350 sanitary professionals participated. The process of citation, structured formation and activation of the patients, started in May 2018, in a formalize procedure in the hospital services, included in the study.

The integral system of following up was designed in four steps:

1. Authorizations: the apply form of clinical data and indication for the monitoring system.
2. Registry: unequivocal identification in two registration Platforms(the APHS corporate and Free View).
3. Follow-up: extraction and loading of aggregate glucose data
4. Evaluation: analysis of clinical information

The processing and discharge of the data from glucometric analysis from MFG system, in the digital clinical history of the children, is scheduled every three months.

Results: A total of 2674 pediatric patients affected of type 1 diabetes, are registered and incorporated pattern, that register 3850560 glucose data every day, and the link to digital clinical history of 37436 of variables every three monthly Data mining is possible at various levels of disaggregation, individual-professional, hospital services, and regional, from the Integral Plan of Diabetes in Andalusia.

Conclusions: A whole system of clinical follow-up in diabetic pediatric patients and users of the MFG System has been set successfully up, in the Andalusia Public Health System. This allows the definition of cohorts, for the study of health result, that include the integration of glucose data in the digital clinical history. It brings an opportunity for a technological organized innovation.

P1-332

Targeted next-generation sequencing demonstrates high frequency of MODY in Russian children

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Background: Maturity-onset diabetes of the young (MODY) is a heterogeneous group of disorders characterised by autosomal dominant type of inheritance and caused by genetic defects leading to dysfunction of pancreatic beta-cells. At least 13 types of MODY have been described in the literature, the most frequent of which are MODY types 1–3. The frequency of different MODY types in children in Russia has not been studied before.

Objective: To evaluate the contribution and molecular spectrum of mutations among MODY genes in Russian patients using a targeted NGS.

Methods: 796 patients with MODY phenotype (388 males, 408 females) were included in the study according to the inclusion criteria (diabetes or intermediate hyperglycemia; GAD, IAA, ICA, IA2 negative; preserved C-peptide secretion). ‘Diabetes panel’ genes were sequenced using a custom Ion Ampliseq gene panel and PGM semiconductor sequencer (Ion Torrent). Interpretation of the sequencing results and assessment of the pathogenicity of sequence variants were performed according to the ACMG guidelines (2015).

Results: 280 different sequence variants (all heterozygous) were identified in 443 patients (55.7%): 171 (61.1%) were classified as pathogenic, 55 (19.6%) - likely pathogenic and 54 (19.3%) variants of uncertain significance. The majority of variants were detected in *GCK* gene (34.2%, n=272/796): 145 variants were pathogenic, 29 were likely pathogenic, 2 - uncertain significance. Different sequence variants were detected in *HNF1A* (n=38/796, 4.8%), *ABCC8* (n=24/796, 3.0%), *HNF1B* (n=15/796, 1.9%), *HNF4A* (n=14/796, 1.8%), *KLF11* (n=8/796, 1.0%), *PAX4* (n=8/796, 1.0%), *PDX1* (n=5/796, 0.6%), *NEUROD2* (n=3/796, 0.4%), *INS* (n=3/796, 0.4%) *KCNJ11* (n=2/796, 0.3%). 24 patients (3.0%) showed mutations in 2 or 3 genes, 6 patients (0.8%) had 2 mutations in the same gene.

Conclusion: Targeted NGS in patients with MODY phenotype showed frequent sequence variants (55.7%) in genes associated with MODY. MODY2 was the most prevalent monogenic type of diabetes (34.2%) in our cohort. Some cases with different degrees of glucose intolerance were associated with digenic/oligogenic defects.

Abdominal fat distribution assessed by abdominal CT scan in adolescents with type 2 diabetes mellitus

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Background: Abdominal fat distributions are reportedly strongly associated with metabolic risks in type 2 diabetes mellitus. However, research on fat distribution in adolescents with type 2 diabetes mellitus has been limited.

Aim: To investigate fat distribution characteristics in adolescents with type 2 diabetes mellitus for comparison to those with simple obesity in Japan.

Design/Methods: Sixty-one adolescents 10 to 15 years of age with simple obesity or type 2 diabetes mellitus, who visited our

outpatient clinics between 2002 and 2018, were enrolled in this study with ethics approval. Simple obesity was defined as a BMI $\geq 95^{\text{th}}$ percentile without. Serum lipids, ALT and HbA1c were measured without fasting. Visceral fat area (VFA) and subcutaneous fat area (SFA) were investigated using umbilical level CT scans. Subjects were classified into 2 subgroups: simple obesity group (n=38) or the type 2 diabetes mellitus group (n=23).

Results: Comparisons between the 2 groups are shown in Table 1. VFA and the ratio of VFA to SFA (V/S ratio) were significantly higher in the type 2 diabetes mellitus group than in the simple obesity group (VFA (cm^2): 74 vs 89.2, p=0.0400, V/S ratio: 0.2 vs 0.32, p<0.0001). SFA was significantly lower in the type 2 diabetes mellitus group than in the simple obesity group (SFA (cm^2) 357 vs 260, p= 0.0076). VFA and SFA correlated with systolic blood pressure (p=0.0009, 0.0099, respectively), ALT (p=0.0486, 0.0486, respectively), total cholesterol (p=0.0178, 0.0032, respectively), and non-HDL cholesterol (p=0.0065, 0.0010, respectively) in the type 2 diabetes mellitus group.

Conclusion: The abdominal fat distributions in type 2 diabetes mellitus differ from those in simple obesity, in adolescent subjects. VFA and SFA correlated with the metabolic parameters in adolescents with type 2 diabetes mellitus.

Table 1. Median (range) of Group Characteristics

	Simple obesity (n=38)	Type 2 diabetes mellitus (n=23)	p-value
Age (years)	12 (10-15)	12 (10-15)	0.6794
Sex (%Male)	52	52	0.9723
BMI %tile	99.1 (95.6-99.9)	97.9 (88.1-99.9)	0.1348
Systolic blood pressure (mmHg)	110 (93-146)	116 (101-149)	0.0692
Diastolic blood pressure (mmHg)	63 (46-78)	67 (54-89)	0.0451*
ALT (U/L)	32 (10-282)	50.5 (13-251)	0.0426*
Total cholesterol (mg/dL)	163 (126-253)	192.5 (125-230)	0.0863
HDL cholesterol (mg/dL)	47.5 (30-76)	44 (26-49)	0.0267*
non-HDL cholesterol (mg/dL)	123 (73-207)	146 (88-187)	0.0344*
HbA1c (%)	5.6 (5.3-6.1)	8.3 (6.1-14.5)	<0.0001*
VFA (cm^2)	74 (25-138)	89.2 (33-206)	0.0400*
SFA (cm^2)	357 (198-619)	260 (94-605)	0.0076*
V/S ratio	0.20 (0.09-0.38)	0.32 (0.20-0.76)	<0.0001*

* p<0.05

Fat, Metabolism and Obesity

P1-334

ADCY3 genetic variants in Cypriot obese children

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Background: The adenylate cyclase 3 (ADCY3) gene encodes a membrane-associated protein involved in the formation of cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). This gene seems to be involved in the regulation of several metabolic processes and has been recently associated to pathophysiological metabolic conditions. Several ADCY3 variants have been linked with obesity in children.

Methods: 33 children of Cypriot origin diagnosed with obesity or severe obesity were analysed by Sanger sequencing for defects in the ADCY3 gene and its proximal intronic regions.

Results: Eight previously reported variants (6 synonymous and 2 missense) and one novel missense variant have been identified in the ADCY3 gene. The novel variant p.Leu117Met has not been previously reported in patients with obesity and was identified in two patients. Additionally, 5 previously reported variants and 1 novel variant have been detected in the intronic region of ADCY3.

Conclusions: Thirteen previously reported and 2 novel variants have been identified in our study. Our results confirm the presence of ADCY3 variants among Cypriot children diagnosed with obesity and therefore provide evidence of a possible link with the susceptibility of the disorder. Functional studies of variant p.Leu117Met will further elucidate its role in the pathophysiology of the disorder.

P1-335

The relationship between serum neurotensin levels and metabolic parameters and eating behavior in obese children

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Introduction: Neurotensin is a 13 amino acid peptide with central and intestinal effects. It has been shown to decrease intestinal and gastric motility, increase the absorption of fat by regulating the release of pancreas and bile acid. In addition, it is reported that there is also an anorexigenic effect of the neurotensin released from the central nervous system. In the literature, conflicting results related to serum / plasma neurotensin levels were reported in experimental and adult obese studies.

Objective: In this study, we aimed to evaluate the effect of serum neurotensin level (i) on metabolic and anthropometric parameters in obese children, (ii) its role in binge eating disorder patogenesis and (iii) on food consumption / preference.

Materials and Methods: The study included adolescents with a body mass index (BMI)> 95p who presented with weight gain between 12-17 years of age and healthy adolescents with a BMI of 3 artı \pm 5p, similar in age and gender. Anthropometric measurements and biochemical analyzes [fasting blood glucose, insulin, lipid profile, ALT, insulin resistance, serum neurotensin, ghrelin and leptin levels] were performed in all cases. Body fat analysis was evaluated with bioelectric impedance device. In all cases, the presence of binge eating disorder (TYB) and three-day food consumption were evaluated.

Results: 65 obese (32 girls, 14,6 ± 1,4 years) and 65 healthy adolescents (32 girls, 14,6 ± 1,5 years) were included in the study. In obese group, BMI, BMI standard deviation score (SDS), waist circumference, fat percentage, fat mass, fasting insulin, insulin resistance index, triglyceride, leptin and neurotensin levels were significantly higher and ghrelin level was significantly lower than the control group. When the levels of leptin, ghrelin and neurotensin were compared in terms of insulin resistance and the presence of TYB in the obese group, no statistically significant difference was found. No significant difference was found in the relation of serum neurotensin level with anthropometric, metabolic and nutritional consumption levels in obese and control groups.

Conclusion: Although the high neurotensin in obese patients has a role in the etiopathogenesis of obesity by increasing intestinal effect (by increasing lipid absorption), it is observed that its effect on TYB is not obvious. The results of this study suggest the presence of hypothalamic neurotensin resistance (increase in compensatory neurotensin) despite the high neurotensin level and no anorexigenic effect detected in obese patients

Genomic knowledge as the powerful tool to understand the obesity

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Obesity, with its complications, emerges as a major contributor to the global health burden becoming pandemic. It's an extremely complex disorder resulting of interaction of biological, social and behavioural factors that cause increase in food intake and reduction in energy expenditure. Although few monogenic forms and indeed several susceptibility loci have been described, the molecular basis underlying early onset obesity remain largely unknown. GWAS revealed consistent association between SNPs with BMI and fat-mass, but cannot demonstrate the undoubted causality, and elucidating the culprit events continues to be challenging, especially when it's not known the way in which variants primarily act. To expand our knowledge, we performed WES in 30 strictly clinical classified Caucasian probands with severe early-onset obesity. We screened a set of 80 responsible/susceptibility genes for syndromic/monogenic forms, including ones belonging to pathways linked to obesity development. We identified potentially pathogenic variants in 75% of our cases. 5 cases presented a single variant in genes related to increase of BMI/WHR, 3 patients had variants in hypothalamic leptin-melacortin pathway, whereas remaining cases showing complex genetic background with mutations in 2/more genes. WES analysis results allowed us to plan a tailored treatment in patients with family history of diabetes, hepatic steatosis and severe obesity who presented pathogenic variant in *SH2B1*, leaded significant weight loss. The systematic discovery of rare variants in complex diseases suggests that the reverse-strategy is fruitful for assigning pathogenic effects of several genes simultaneously; the genotype-first approach will be able to identify clinically recognizable phenotypes.

How does Clusters of Parental Characteristics Influences Offspring Adiposity: A Prospective Study

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Introduction: Childhood obesity rates have increased exponentially in the past three decades. Parental characteristics, such as weight status, physical activity (PA), education and smoking habits have been identified individually as being potential determinants of offspring obesity. However, no prospective studies have examined the joint impact of parental lifestyle habits on their offspring's adiposity. We identified clusters of parental characteristics, and estimated their influence on offspring adiposity in late adolescence.

Methods: Data stem from the QUALITY Cohort, a longitudinal study of children with at least one obese parent. Children were evaluated at 8-10y (n=630), 10-12y (n=564), and 15-17y (n=377). Parental smoking habits, PA and education were self-reported. Weight and height were obtained and body mass index (BMI) was calculated. Cluster analysis was performed on 209 families with complete data across all 3 evaluation cycles. We performed cluster analysis on mothers and fathers separately using partitioning around medoids (PAM) to identify parental phenotype clusters based on 4 parental characteristics (BMI, PA, education and smoking habits). Linear regressions, adjusted for child age, sex and Tanner stage, were used to assess associations between clusters (mothers and fathers) and measures of childhood adiposity (BMI z-score) at 15-17y.

Results: Three clusters were identified among mothers and four clusters among fathers. Mothers in cluster 1 (n=18) were obese, less educated, smoked, and tended to be more active; cluster 2 (n=109) were overweight, educated and non-smokers; cluster 3 (n=82) were overweight, less educated, non-smokers and tended to be less active. Fathers in cluster 1 (n=109) were less educated and non-smokers, cluster 2 (n=68) were educated and non-smokers, cluster 3 (n=23) were less educated and smokers and cluster 4 (n=9) were older, educated and smokers.

Children of obese, less educated and smoking mothers (cluster 1) had higher adiposity measurements compared with children of overweight, educated, non-smoking mothers (cluster 2), with an increase in BMI z-score of +0.94 (95% CI: 0.35-1.53); p=0.002. Child adiposity measurements were comparable across father phenotype clusters.

Conclusions: Targeting obese and less educated mothers who smoke to promote the adoption of healthier lifestyle habits may be effective at preventing later adiposity in their offspring.

P1-338**Continuous Score of Metabolic Syndrome (sSMP) in Chilean Pediatric Population is Associated with Insulin Resistance Parameters and Subclinical Endothelial Inflammation**

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Introduction: The dichotomous nature of the definition of Metabolic Syndrome (MS) in both children and adults can under-diagnose subjects at risk and prevents adequate follow-up of therapeutic interventions. Recently, a continuous score of MS (sSMP) was validated in the pediatric population based on the IDF criteria for a population > 16 years.

Objectives: To apply sSMP in a Chilean pediatric population cohort and correlate it with parameters of Insulin Resistance and subclinical endothelial inflammation.

Subjects and Methods: We studied 385 subjects (47.2% women), of 11.5 ± 2.8 years of age. Anthropometry, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were performed. Insulin, glycemia, triglycerides, HDLcol, LDLcol, GOT, GPT, IL6, PAI-1, usCRP, TNF-alpha and adiponectin were determined and the HOMA-IR was calculated. The sSMP was calculated according to the following formula: $sSMP = 2x \text{ waist} / \text{height} + \text{Glicemia} (\text{mmmol/l}) / 5.6 + \text{Triglycerides} (\text{mmol/l}) / 1.7 + \text{SBP} / 130 - \text{HDLcol} (\text{mmol/l}) / 1.02$. Pearson correlation (R) was used to evaluate associations between the variables.

Results: 41.51% were overweight and 17.4% were obese. The waist / height ratio was 0.51 ± 0.07 , SBP 112.5 ± 13.7 mmHg, blood glucose 85.8 ± 6.2 mg / dL, TG 77 ± 53.6 mg / dL, HDL 50.4 ± 12.1 mg / dL. sSMP correlated positively with age ($R = 0.25 **$), BMI ($R = 0.5 **$), PAD ($R = 0.28 **$), GPT ($R = 0.268 **$), Insulin ($R=0.39**$), glycemia ($R=0.235**$), HOMA ($R=0.398**$), IL6 ($R=0.13*$), PAI-1 ($R=0.28 **$), usCRP ($R=0.22**$), adiponectin ($R=-0.3 **$). ** $p<0.001$, * $p<0.05$.

Conclusions: To our knowledge, this is the first study that validates sSMP and its association with parameters of Insulin resistance and subclinical endothelial inflammation in the pediatric population. The sSMP constituted by a numerical value represents a practical and simple way of predicting children and adolescents at cardiometabolic risk, escaping the dichotomous nature of the classic definition of MS. Future studies will be necessary to establish a cut-off point for the sSMP, capable of individually validating this prediction.

P1-339**Elevated high-sensitivity C-reactive protein level is associated with prediabetes and adiposity in Korean children and adolescents**

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Objectives: Obesity is a chronic low-grade inflammatory condition that increases the risk of cardiovascular disease. Elevated high-sensitivity C-reactive protein (hs-CRP) has been associated with cardiovascular disease, type 2 diabetes, and metabolic syndrome in adults. We investigated whether hs-CRP represents a risk factor for obesity and cardiometabolic diseases in Korean children and adolescents using nationally representative data.

Methods: A total of 1,138 youths (54.1% boys and 45.9% girls) aged 10–18 years who were registered in the Korea National Health and Nutrition Examination Survey (2015–2016) were included. Anthropometric, biochemical, nutritional, and physical activity data were collected. Participants were divided into 3 hs-CRP tertiles. Abdominal obesity, impaired fasting glucose, elevated triglyceride, decreased high-density lipoprotein (HDL) cholesterol, elevated blood pressure, and prediabetes (glycated hemoglobin [HbA1c] 5.7–6.4%) were compared between hs-CRP tertiles in both sexes.

Results: The ranges of each hs-CRP tertile were <0.3 mg/L, 0.31–0.5 mg/L, and ≥ 0.5 mg/L. Hs-CRP was positively associated with the body mass index (BMI) z-score ($P < 0.001$) and HbA1c ($P = 0.012$), and negatively associated with HDL cholesterol level ($P = 0.045$), after adjusting for age, sex, BMI, white blood cell count, physical activity, and nutritional factors. The upper tertile of hs-CRP was associated with obesity (adjusted odds ratio [aOR] 11.93, $P < 0.001$) and prediabetes (aOR 3.10, $P = 0.002$).

Conclusions: Hs-CRP is associated with BMI z-score, HbA1c, and HDL cholesterol in Korean children and adolescents, and can hence be a reliable indicator for adiposity, prediabetes, and abnormal lipid metabolism in pediatric populations.

P1-340**Secular change in waist circumference and waist-height ratio in Korean children and adolescents over 10 years and effort to identify optimal cutoff for cardiometabolic risk**

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Purpose: The aims of this study were to identify the secular changes of WC and WHR, to compare WC with the prior Korean reference, to confirm the distribution of mean WHR values by age

and sex, and to determine if WHR cutoff value of 0.5 is an appropriate predicting factor of cardiometabolic risk in childhood, using nationally representative data in children and adolescents.

Methods: We performed a retrospective, cross-sectional analysis of data from 13,257 children and adolescents (boys 6,987 and girls 6,270) aged 6-18 years who were included in the 3rd to 6th Korea National Health and Nutrition Examination Survey (KNHANES, 2005-2015). Receiver operating characteristic (ROC) curve analysis was used to identify the optimal threshold of WHR between 13 to 18 years of age in predicting the cardiometabolic risk factor including abdominal obesity, elevated BP, hyperglycemia, elevated HbA1c, High triglyceride, and low HDL cholesterol. The areas under the ROC curves (AUC) were obtained for each parameter.

Results: There were no secular change of mean WC and WHR by age between KNHANES 4 waves without significant difference. Mean WC increased with age in both sexes. Mean WC was significantly higher in boys than girls in all ages ($P<0.001$). Compared with previous 2007 Korean National Growth Charts, the mean WC tended to be lower for all ages. Mean WHR falls within the range of 0.421-0.451 for each sex and age. Mean male WHR was significantly greater than that of females aged 6 to 12 years ($P<0.001$). However, after 13 years old, there was no difference between WHR of boys and girls. The ROC curve analysis was performed between 13 to 18 years. The optimal WHR cutoff values capable of predicting all cardiometabolic risk factors were under 0.5 with higher sensitivity and negative predictive values. The optimal cutoff value for abdominal obesity was the highest as 0.480 with an AUC of 0.985 (sensitivity, 97.6%; specificity, 91.3%). The other optimal WHR cutoff values for cardiometabolic risk factors ranged from 0.442 to 0.462 with AUC from 0.545 to 0.735.

Conclusion: There was no secular change in WC and WHR over 10 years. The optimal WHR cutoff for abdominal obesity, 0.48 would be helpful to diagnose and to manage obesity in Korean 13-18 years old adolescents, preventing obesity related cardiometabolic complications.

P1-341

ANGPTL2 and ANGPTL3 in children with obesity and metabolic syndrome

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Introduction: Angiopoietin-like proteins (ANGPTLs) play critical roles in metabolism and are implicated in metabolic consequences of obesity. ANGPTL2 is a key adipocyte-derived inflammatory mediator that links obesity to systemic insulin resistance. ANGPTL3 directly regulate lipid, glucose and energy metabolism independent of angiogenic effects. In this study, we aimed to investigate the levels of ANGPTL2 and 3 in obese children and adolescents and their association with metabolic parameters.

Methods: Seventy children and adolescents (35 obese and 35 age- and gender-matched control subjects), were selected after thorough clinical evaluation and anthropometric measurements. Serum ANGPTL2 and 3 and insulin were assessed using ELISA, and insulin resistance (IR) was calculated by the homeostatic model assessment of insulin resistance (HOMA-IR). Fasting plasma glucose (FPG), triglyceride, total cholesterol (TC), LDL-C and HDL-C were also measured.

Results: ANGPTL2 and 3 levels were significantly elevated in obese children compared with controls; however, they were not significantly different in obese children with or without IR. ANGPTL3 was significantly higher in children with metabolic syndrome (MetS) compared to those without MetS. Both ANGPTL2 and 3 were positively correlated with BMI, TC and LDL-C as well as systolic (SBP) and diastolic (DBP) blood pressure. In partial correlation, controlling for BMI, the relationship between ANGPTL3 and both SBP and DBP remained significant. A significant positive correlation was found between ANGPTL2 and ANGPTL3 which remained significant after adjusting for BMI.

Conclusion: Elevated levels of serum ANGPTL2 and 3 and their relationship with metabolic parameters, especially blood pressure, suggests that these two proteins might be involved in the development of obesity-associated metabolic syndrome and endothelial dysfunction.

P1-342

Can Increased First Hour Glucose Concentration in OGTT Be a New Indicator in Projecting Metabolic Profile?

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Aim: Recent studies have shown that the first hour glucose concentration of ≥ 155 mg / dL in the oral glucose tolerance test (OGTT) in adults with normal glucose tolerance (NGT) may be a strong marker for the development of diabetes, and also an increase in subclinical inflammation, insulin resistance, dyslipidemia and serum transaminases. These results indicate that adults with NGT have increased risk of developing cardiovascular disease and non-alcoholic liver disease as well as type 2 diabetes. Research done on children is limited, and in our study, it was aimed to investigate the relationship between increased first hour glucose concentration during OGTT and metabolic parameters in children with NGT.

Material-Methods: The records of 193 obese / overweight children aged 9-18 years who underwent OGTT were retrospectively evaluated. NGT: Fasting plasma glucose was defined as <100 mg / dl, second hour blood glucose <140 mg / dL. 143 cases with NGT were included in the study. Group 1 with OGTT first hour glucose concentration <155 mg / dL and group 2 with first hour glucose concentration ≥ 155 mg / dL. BMI, hypertension, lipid profile, insulin resistance, serum transaminases, uric acid level and hepatosteatosis were compared among the groups.

Results: The mean age of our cases was 13.6 ± 2.2 years, 64.3% female and 35.7% male. 8.4% were Tanner stage 1, 49.7% were Tanner stage 5. In group 2, systolic, diastolic blood pressure, serum triglyceride, uric acid, ALT, HbA1C and HOMA-IR levels were significantly higher whereas HDL level was significantly lower ($p < 0.05$). In group 2, hepatosteatosis was detected in all cases except one patient; group 1 had a significantly lower rate of hepatosteatosis ($p < 0.05$). OGTT first hour glucose concentration was positively correlated with acanthosis nigricans, triglyceride, uric acid, ALT, hepatosteatosis, HbA1C and HOMA-IR while it was negatively correlated with HDL ($p < 0.05$).

Conclusion: Children with first hour postload plasma glucose concentration of ≥ 155 mg / dl, despite being defined as normal according to the ADA criteria, have a worse metabolic profile in terms of cardiovascular disease and the development of type 2 diabetes. OGTT first hour glucose concentration should be considered as a valuable marker in identifying risky children, even if they have NGT.

Key Words: One hour postload plasma glucose, Children, Adolescents, Cardio-metabolic risk.

P1-343

Perinatal features of Prader-Willi syndrome: a Chinese cohort

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Background: Prader-Willi syndrome (PWS) is a rare complex genetic disorder caused by an absence of expression of imprinted genes on the paternally derived chromosome 15q11-q13 region. This study aimed to characterize the perinatal features in a cohort of Chinese individuals with PWS.

Methods: We analyzed anonymous data of 134 patients from the PWS Registry in China. Perinatal and neonatal presentations were analyzed, and compared between the two PWS genetic subtypes. We also compared the perinatal features of PWS patients with the general population and other previous reported large cohorts from France, UK and USA.

Results: This study included 134 patients with PWS (115 patients with 15q11-q13 deletion and 19 with maternal UPD). High mean maternal age was found in this cohort (30.5 vs. 26.7) comparing with the general population. 88.6% of mothers reported a decrease of fetal movements. 42.5% and 18.7% of mothers had polyhydramnios and oligohydramnios during pregnancy, respectively. 82.8% of the patients were born by caesarean section. 32.1% of neonates had birth asphyxia, 98.5% had hypotonia and 97.8% had weak cry or even no cry at neonatal period. Feeding difficulty existed in 99.3% of the infants, and 94.8% of them had failure to thrive. 69.4% of the infants ever used feeding tube during hospitalization. However, 97.8% of them discontinued tube feeding after discharged home. Maternal age, maternal pre-pregnancy weight and BMI were significantly higher in the UPD group (all $P < 0.05$).

Conclusions: PWS should be highlighted for differential diagnosis for infants with following perinatal factors including polyhydramnios, intrauterine decreased fetal movements, cesarean section, low birth weight, feeding difficulty, hypotonia, and failure to thrive. Higher maternal age may be a risk factor for PWS, especially for UPD, and further studies for the mechanism of PWS are required.

P1-344

Abstract withdrawn

P1-345

ANGPTL-4 in children and adolescents: relation to gender, puberty and obesity

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Introduction: Preclinical models demonstrated that Angiopoietin-like protein 4 (ANGPTL-4) regulates lipid metabolism and affects energy homeostasis. However, no data exist regarding its involvement in childhood and adolescence, periods of life with important metabolic changes.

Objectives: We aimed to investigate circulating levels of ANGPTL-4 in children and adolescents and its relationship with gender, puberty and obesity.

Material and Methods: Plasma ANGPTL-4 levels were analysed in 150 Caucasian children (72) and adolescents (78). The sample was classified as obese (percentile \geq 95th; n = 77) and normal-weight (n = 73) by using the standard definition from Cole et al. The concentration of ANGPTL-4 was measured using an ELISA kit (Human ANGPTL4 ELISA kit SK00309-01; Aviscera Bioscience) and statistical analyses were performed using the SPSS software.

Results: Girls and boys showed similar concentrations in plasma levels of ANGPTL-4. The puberty did not modify the ANGPTL-4 circulating levels. However, ANGPTL-4 was significantly reduced in children and adolescents with obesity compared to lean participants. This reduction was independent of the gender and sexual maturation. Moreover, ANGPTL-4 was negatively correlated with BMI, body weight and waist circumference.

Conclusion: This study reveals that ANGPTL-4 levels are deregulated in children and adolescents with obesity independently of the gender and puberty.

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P1-346

Non-invasive assessment of liver steatosis: usefulness of elastography in obese children – a pilot study

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is diagnosed in up to 60% of overweight children. Diagnosis and management of NAFLD is challenging due to the lack of non-invasive imaging biomarkers. Ultrasound (US) is the most widely non-invasive method used to identify liver steatosis, however it has low sensitivity to detect mild steatosis and to quantify hepatic fibrosis. Liver Elastography (LE) is a non-invasive methodology used to evaluate hepatic stiffness and fat deposition. Few studies have evaluated the reliability of LE in pediatric obesity.

Objectives: 1) To assess hepatic stiffness and shear-wave velocity (SWV) by LE in obese children and adolescents; 2) to compare LE findings with hepatic echogenicity evaluated by conventional US; 3) to evaluate the correlation between hepatic stiffness and clinical and biochemical indices of cardio-metabolic risk.

Methods: Eighty children with simple obesity (55% female, 45% male) were recruited according to the following criteria: no genetic or endocrine causes of obesity; no associated chronic diseases neither chronic therapies. All patients underwent anthropometric, bioimpedimetric and biochemical (lipid profile, oral glucose tolerance test, thyroid, kidney, liver function tests) assessments. HOMA-IR, Matsuda-index, Insulinogenic index, oral disposition index, insulin and glucose Areas Under the Curves were evaluated. In each patient, both conventional liver US and LE were performed by two radiologists; stiffness and SWV were measured.

Results: Mean age and BMI SD were 11.6 ± 2.3 years and 3 ± 0.6 , respectively. Mean age at onset of obesity was 5.6 ± 2.6 years. Liver steatosis was documented by conventional US in 16 patients (mild steatosis in 56%, moderate in 37.5%, severe in 6%). Mean stiffness was 10.66 ± 1.9 kPa; mean SWV was 1507.5 ± 43.2 m/s. The presence of steatosis was directly correlated to waist circumference ($p=0.036$), total cholesterol ($p=0.014$), triglycerides ($p=0.043$), ALT ($p=0.040$), AST ($p=0.006$), GGT ($p=0.000$), triglycerides/HDL-ratio ($p=0.024$). At the multivariate regression analysis, total cholesterol ($p=0.040$), triglycerides ($p=0.041$), triglycerides/HDL-ratio ($p=0.037$) were independent predictors of steatosis. No correlations were demonstrated between presence of steatosis and glucose metabolism indices.

Stiffness and SWV were not significantly correlated with any anthropometric, bioimpedimetric and biochemical variables.

Conclusions: In obese children, the presence of steatosis is significantly influenced by lipid profile alterations. In our cohort, stiffness and SWV did not correlate with presence of steatosis, severity of obesity, anthropometric, bioimpedimetric, biochemical indices of cardio-metabolic risk. LE does not seem to provide additional information compared to conventional US, probably because NAFLD is not usually associated with hepatic fibrosis in pediatric obesity.

P1-347

Precocious Pubarche in Spinal Muscular Atrophy Patients with Severe Sarcopenia

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Context: Spinal muscular atrophy (SMA) is an autosomal recessive inherited disease characterized by degeneration of anterior horn cells of the spinal cord and brainstem resulting in variable degrees of muscular atrophy and proximal muscle weakness. In December 2016, nusinersen was FDA-approved for the treatment of SMA in pediatric and adult patients. The introduction of this therapeutic modality has provided a platform for professional medical-care providers in our national neuromuscular center. To the best of our knowledge, this is the first report on endocrine manifestations in patients with severe forms of SMA.

Aims: To identify endocrine characteristics of SMA patients with precocious pubarche.

Methods: Real-life data in 62 SMA patients (24 type 1, 21 type 2, 17 type 3) were collected during routine clinic visits prior to nusinersen intervention. Anthropometric measurements and pubertal stage were determined by pediatric endocrinologists. Self-reported onset of puberty was documented for patients in puberty/fully pubertal. Laboratory evaluation included kidney and liver function tests, measures of glucose metabolism (fasting blood glucose and insulin levels, calculation of Homeostatic Model Assessment of Insulin Resistance [HOMA-IR]), basal androgen profile levels (testosterone, 17-hydroxyprogesterone, androstenedione and dehydroepiandrosterone sulfate) and as clinically indicated - Synacthen stimulation testing for the diagnosis of adrenal enzymatic disorders.

Results: Twenty-four percent (15/62) of the studied cohort had precocious pubarche, 45.9% (11/24) with SMA type 1, and 19% (4/21) with SMA type 2. One of the type 2 patients with rapid progression of adrenarche was diagnosed with non-classic congenital adrenal hyperplasia by Synacthen test and was excluded from analysis. Fourteen patients with precocious pubarche (mean age at onset 3.9 ± 2.8 years), without rapid progression had no other clinical signs or laboratory evidence of hyperandrogenism. SMA patients with precocious pubarche were characterized by significantly higher HOMA-IR levels (4.1 ± 2.9 vs. 2.4 ± 1.9 , $P < 0.001$) and significantly lower creatinine levels (0.09 ± 0.04 vs. 0.20 ± 0.12 , $P = 0.001$) compared to those without precocious pubarche. Body mass index SDS / weight-for-length SDS of the study cohort was relatively low (-1.34 ± 2.65), with no significant differences between groups.

Conclusions: Our findings suggest that isolated precocious pubarche is a common clinical manifestation in the severe types of SMA with markedly decreased muscle mass. Isolated precocious pubarche in those patients is characterized by increased insulin resistance without laboratory evidence of hyperandrogenism. Further studies are warranted to delineate the role of sarcopenia and body fat/muscle imbalance in extreme underweight patients with precocious pubarche.

P1-348

Evaluation of the Relationship between Serum Uric Acid Level and Cardiometabolic Risk in Obese Children and Adolescent

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Background: In adult studies, serum uric acid level (SUA) has been shown to be associated with cardiometabolic anomalies of metabolic syndrome such as insulin resistance, hypertension, increased carotid intima thickness, and hyperuricemia is considered as an independent risk factor for atherosclerosis and cardio-

vascular disease. Early cardiovascular changes in obese children and studies on the relationship between metabolic syndrome and hyperuricemia are quite limited. In our study, it was aimed to evaluate the relationship between SUA level and obesity comorbidities in obese children and adolescents and cardiometabolic risk.

Material-Methods: The records of 144 obese patients aged 10-18 years were evaluated retrospectively. According to age and sex, SUA level was <95 percentile group 1 and SUA level was ≥95 percentile group 2. Body mass index (BMI), hypertension, lipid profile, insulin resistance, serum transaminases, hepatosteatosis, ambulatory blood pressure measurements (ABPM), and left ventricular hypertrophy based on the measurement of left ventricular mass in echocardiography were compared between the two groups.

Results: In group 2, BMI SDS, serum triglyceride, AST, ALT levels and hepatosteatosis were significantly higher, whereas HDL level was significantly lower. In OGTT, 60, 90 and 120 min glucose levels and 120 min insulin levels were significantly higher in Group 2. No differences were found between groups HbA1C and HOMA-IR. When the presence of hypertension was evaluated; both office and ABPM measurements were significantly higher in group 2. Left ventricular hypertrophy was found in 38.2 % of the cases in group 2 and the mean left ventricular mass index was significantly higher with $38.05 \pm 11.39\text{g/m}^2$.

Conclusions: The identification of children with a high risk of cardiometabolic is extremely important for the prevention of complications related to childhood obesity. We suggest that serum uric acid levels may be an early marker of obesity comorbidity and cardiovascular dysfunction in obese children and adolescents.

Keywords: Childhood obesity, uric acid, cardiometabolic risk

P1-349

Prevalence of dyslipidemia in Korean youth over 10 years: data from the Korea National Health and Nutrition Examination Survey 2008-2017

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Objectives: Dyslipidemia begins and continues in youth and is a major risk factor for adult-onset cardiovascular disease. The aim of this study was to investigate the prevalence and trend of dyslipidemia in Korean youth and its trends for 10 years.

Methods: Study subjects were Korean youth aged 10-18 years who participated in the Korea National Health and Nutrition Examination Survey (KNHANES). A total of 7,466 eligible participants (3,962 boys, 53.2%) with available fasting lipid profile were enrolled. The KNHANES data for 10 years from 2008 to 2017 were divided into five groups at two-year intervals (2008-09, 2010-11, 2012-13, 2014-15, 2016-17). Dyslipidemia was defined using the 2011 National Heart, Lung and Blood Institute (NHLBI) criteria: hypercholesterolemia, total cholesterol $\geq 200\text{ mg/dL}$; hypertriglyceridemia, triglyceride $\geq 130\text{ mg/dL}$; hypo-HDL-cholesterolemia, HDL cholesterol $< 40\text{ mg/dL}$; hyper-LDL-cholesterolemia, LDL cholesterol $\geq 130\text{ mg/dL}$; and hyper-non-HDL-cholesterolemia, non-HDL cholesterol $\geq 145\text{ mg/dL}$.

Results: The prevalence of hypercholesterolemia was 6.7% in 2008-09, 6.5% in 2010-11, 6.6% in 2012-13, 7.8% in 2014-15 and 10.7% in 2016-17 (P for trend <0.001). The prevalence of hypertriglyceridemia was 14.7% in 2008-09 and 13.0% in 2016-17 (P for trend = 0.389). The prevalence of hypo-HDL-cholesterolemia was 16.4% in 2008-09 and 10.2% in 2016-17 (P for trend <0.001). The prevalence of hyper-LDL-cholesterolemia was 5.4% in 2008-09 and 7.6% in 2016-17 (P for trend = 0.080). The prevalence of dyslipidemia defined by non-HDL level was 9.0% in 2008-09 and 10.9% in 2016-17 (P for trend = 0.105). In logistic regression analyses, the prevalence of hypercholesterolemia was increasing after adjusting age, sex and body mass index (OR 1.14, 95% CI 1.05-1.22, P <0.001). In contrast, the prevalence of hypo-HDL-cholesterolemia was decreasing tendency after adjusting age, sex, and body mass index (OR 0.82, 95% CI 0.78-0.87, P <0.001). Except for hypo-HDL-cholesterolemia, female predominance was observed.

Conclusion: In Korean youth, the prevalence of hypercholesterolemia showed increasing tendency over the last 10 years. It was obvious especially in female population. However, the prevalence of hypo-HDL-cholesterolemia showed decreasing tendency over the last 10 years. Further research is needed to investigate associated factors with this trend.

P1-350

Metabolic risk in long-term survivors of childhood acute lymphoblastic leukemia

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The aim of this study is to evaluate the modifiable factors of metabolic risk among survivors of childhood acute lymphoblastic leukemia (ALL) treated at a single center in comparison with healthy controls.

Forty-seven long-term survivors, aged 9-32 years were compared to 35 age- and sex-matched controls. Anthropometric features and laboratory findings were assessed. The body composition was measured by Dual-energy X-ray absorptiometry (DEXA). The physical activity (PA) was assessed by questionnaires and interview.

After a median follow-up of 136 months overweight/obesity was present in 48.9% of survivors. BMI Z-score and waist circumference were significantly higher among survivors under 18 years of age (0.95 ± 0.7 vs -0.23 ± 0.9 , p=0.001 and 78.6 ± 8.9 cm vs 65.9 ± 9.0 cm, p=0.001, respectively) and among males above 18 years (0.62 ± 1.1 vs -0.50 ± 0.7 , p=0.004 and 95.5 ± 14.8 cm vs

83.1 ± 8.9 cm, p=0.01, respectively), compared to controls of the same age groups. Younger (under 18) survivors and older (above 18) male survivors, as well these with cranial radiotherapy of 24 Gy, had significantly higher percentage of fat and fat mass index as compared to controls. Fifty-seven percent of young women presented with normal weight obesity after treatment. At least one abnormality of the lipid panel was observed more frequently among survivors than controls (59.6% vs 25.7%, p=0.001); two and more abnormalities were more likely present in male than female survivors (32% vs 4.5%, p=0.01). The rate of metabolic syndrome differed significantly between survivors and controls (14.9% vs 0%, p<0.007). ALL survivors, especially females, were engaged in weekly sport activities about twice less frequently than controls (2.2 ± 2.6 vs 4.0 ± 3.4 , p=0.005), fewer of them had weekly PA adequate to recommendations (44% vs 69%, p=0.03) and most had longer daily screen time (194 ± 103 min vs 141 ± 72 min, p=0.01).

Even at a relatively young age, survivors of childhood ALL develop an unfavorable long-term cardiovascular profile. Early identification and aggressive management of traditional risk factors in this population would reduce the overall metabolic risk.

P1-351

Congenital generalized lipodystrophy type 4 - New mutation in the CAVIN1 gene

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Introduction: Congenital generalized lipodystrophies (CGL); autosomal recessive disorders characterized by dyslipidemia and almost complete absence of body fat associated with insulin resistance. It develops due to mutations in AGPAT2, BSCL2, CAV1, PTRF, PCYT1A and PPAR, genes. CGL type 4 results from PTRF-CAVIN gene mutation. Unlike classical CGL, myopathy, flat and skeletal muscle hypertrophy, heart rhythm disorders (sudden death) and skeletal abnormalities are seen.

Case: 9 years and 4 months old male patient. She presented with weakness, muscle weakness, difficulty in walking, and elevation of blood fat. The patient's history revealed a 34-weeks age of 2800 g, birth, pyloric stenosis at 40 days of age and a 5-years-old undescended testis surgery. The mother and father were cousins of the 1st degree and he received LT4 treatment in the other center from 7 months to 6 years of age due to hypothyroidism. Physical examination weight: 31.7 kg (50-75p), Height: 143.5 cm (75-90p), dysmorphic appearance, whole body subcutaneous fat tissue deficiency, axial muscle weakness, lumbar lordosis, hypertrophy appearance in muscles, hip, knee and ankle joints had limitation of movement and inability to walk. Fasting serum glucose: 89 mg / dl, insulin: 11.3 IU / mL, HbA1c: 5%, AST: 29 IU / L, ALT: 44 IU / L, Total cholesterol: 150 mg / dL, HDL: 25 mg / dL, LDL: 110 mg / dL, Triglyceride: 455 mg / dL, CK: 746 IU / L. The ECG showed an incomplete right bundle branch block, a frequent atrial ectopic beat in the holter, ventricular tachycardia, and a mild hypertrophy

of the left ventricle in the ECO. In the genetic analysis, homozygous mutation of c.A406T (p.K136X) was detected in the 1st exon of the CAVIN1 gene.

Result: Early diagnosis and treatment of arrhythmias is important because of arrhythmia and sudden death in CGL type 4. Also; In addition to myopathy and cardiac disorders, atlanto axial instability, hepatomegaly, high serum triglyceride level, hyperinsulinism or diabetes, low leptin and adiponectin levels, immunoglobulin A deficiency, and low growth hormone levels are secondary features. A few patients with CGL type 4 have been reported in the literature. The c.A406T (p.K136X) mutation found in our patient is a new mutation. In patients with lipodystrophy, the presence of myopathy and skeletal findings should be investigated and CGL type 4 should be kept in mind. There are fetal rhytm disorders with CGL type 4. So, early diagnosis and treatment should be provided with careful investigation of rhytm disorders.

P1-352

Paediatric patients with type 1 diabetes mellitus exhibit reduced brown adipose tissue heat signature following cold stimulation

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Brown adipose tissue (BAT) is a key component of the body's defence against cold challenge and possesses the ability to convert large amounts of chemical energy to heat, conferred by a unique protein, uncoupling protein (UCP)-1, diverting mitochondrial respiration from the production of adenosine triphosphate. In humans, the largest BAT depot is in the supraclavicular region. Sympathetic nervous system stimulation induces glucose uptake into brown adipose tissue, as does insulin. Despite significant improvements in recent years, people with type 1 diabetes mellitus maintain blood glucose levels higher than healthy controls in order to avoid recurrent hypoglycaemia. In addition, insulin is administered into the peripheral circulation, rather than the portal circulation, altering the balance of peripheral and portal levels. Although hyperglycaemia leads to peripheral insulin resistance in muscle and white adipose tissue, it is not known if the same applies to BAT.

BAT is most abundant in children and adolescents and declines with age. The high ionising radiation required for PET-CT, the previous gold standard imaging method, largely excluded children from prospective studies. We have developed a technique to measure the heat signature of supraclavicular BAT using infrared thermography. We used this technique to measure the supraclavicular temperature of 20 children and young people (CYP) with type 1 diabetes (D) and compared them to 20 healthy controls (C). Characteristics (age, gender, height, weight and BMI) were similar between the groups. Following cold stimulation with a cooling blanket around the right forearm, the CYP with type 1 diabetes had a lower absolute supraclavicular temperature (D: $35.0 \pm 0.6^\circ\text{C}$; C: $35.4 \pm 0.6^\circ\text{C}$; $p < 0.05$) which remained significantly lower when

compared to a sternal reference point (D: $1.8 \pm 0.4^\circ\text{C}$; C: $2.1 \pm 0.5^\circ\text{C}$; $p < 0.05$). There was no difference in the change from pre-stimulation temperature. Supraclavicular temperatures were not associated with measures of either chronic diabetic control (HbA1C) or acute status (blood glucose level).

The relationship between BAT and insulin is complex. In the physiological state, insulin is strongly suppressed by sympathetic nervous system control. Since exogenous insulin is not responsive to the sympathetic nervous system, it is unable to be suppressed following a cold challenge which could be an explanation for the lower stimulated supraclavicular temperature.

P1-353

Evaluation of primary hypertriglyceridemia patients: Etiology, phenotype, treatment

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Introduction: Plasma triglyceride (TG) is formed by an exogenous pathway taken from food and by an endogenous pathway produced from the liver. Primer hypertriglyceridemia occurs by genetic reasons. Higher TG levels occurs in lipoprotein lipase (LPL), ApoC2, ApoA5 gene defects. Secondary hypertriglyceridemia is caused by obesity, insulin resistance, alcohol and some drugs. In that study, we evaluated 10 patients with primer hypertriglyceridemia regards to clinical and genetics.

Method: Evaluated of sex, age, age of diagnosis and lipid levels of diagnosis in this study. Genetic studies were performed. In the follow-up of patients with pancreatitis attack and treatment compliance of patients with pancreatitis attack were examined. The patients were also evaluated for cardiac, ophthalmic examination, thyroid function tests, liver functions and no complications were observed. In diet treatment was arranged restricted from total fat (15% fat of total calorie intake), restricted from long chain fatty acid and rich from medium chain fattyacid. Fat-soluble vitamins and essential fatty acids supplements are provided.

Findings: Age, gender, age at diagnosis, baseline lipid levels, pancreatitis status and genetic results are presented in the table (Table). Our treatment target TG level was determined as 1000 mg/dl and below. Early diagnosed and treated patients were protected from pancreatitis attack. Two patients who have treatment adaptation problem had pancreatitis attack. Liver function tests, thyroid function tests and ECO cardiographies were within normal limits. Lipemia retinalis was detected in two patients.

Results: With this study, we wanted to show that genetic diversity in patients, importance of diet in prognosis, and patients can be protected from possible complications with appropriate treatment

Age	Gender	Starting age of treatment	Blood Lipids (mg/dl) TC/HDL/LDL/TG			Genetics
				Pancreatitis		
4y	M	36 day old	543/ 385/ 203/ 16818	+	c.-3G>A homozygous ApoA5 polymorphism	
1,5 y	F	28 day old	1070/ 257/ 3/ 17265	-	LPL gene, homozygous, new	
1,5y	F	44 day old	421/ 48/ 147/ 1977	-	LPL gene, heterozygote, frame shift mutation, new	
3y	F	42 day old	916/ 156/ 573/ 986	-	LPL gene, homozygous, new	
2,5y	F	27 day old	367/ 102/ 2/ 35000	-	LPL gene, homozygous, new	
16y	F	14 years old	254/ 47/ 143/ 778	-	Being analyzed	
13y	M	12 years old	251/ 59/ 15/ 2550	-	LPL gene, homozygous, new	
13y	M	13 years old	251/ 59/ 15/ 2100	+	Being analyzed	
7m	M	10 days old	886/-/-/ 13400	-	Being analyzed	
6y	F	4 years old	374/ 74/ 8/ 3941	-	LPL gene, homozygous, new	

P1-354

Association between adiposity measures and metabolic variables in children and adolescents with obesity

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Childhood obesity has become a major health issue in the last decades. Moreover, identifying a simple, feasible, and valid screening tool to select subjects at higher risk for obesity-related comorbidities has become a challenge. Current guidelines recommend to use BMI percentile for overweight and obesity diagnosis. However, waist-to-height ratio (WHR) has been associated with the risk of metabolic derangement in children and adolescents with overweight and obesity. In addition, recently, the tri-ponderal mass index (TMI) has been proposed as a better predictor of total adiposity compared to body mass index in children and adolescents. However, in youth, BMI has been shown to be a better predictor of long-term obesity-related comorbidities compared to TMI and subscapular skinfold thickness. In our study we sought to evaluate the association between these three anthropometric indexes and metabolic variables in children and adolescents with overweight or obesity. Therefore, we investigated the association between TMI, BMI-z score, and WHR and glucose and lipid homeostasis parameters in 1397 obese and overweight children and adolescents. All the children underwent an anthropometrical and biochemical evaluation. Glucose homeostasis and insulin sensitivity were assessed by a standard 2-h oral glucose tolerance test. Simple logistic regression analyses were performed to estimate the association between metabolic parameters and anthropometric measures. Generalized Linear Model analyses were conducted between each metabolic parameter and each anthropometric measure adjusting for age, sex, and pubertal stage as second model. Moreover, a third model was performed including all covariates and TMI, BMI-ZS,

and WHR. We observed that in our cohort, overall, WHR was the best predictor for glucose and lipid metabolism parameters followed by TMI and then BMI-z score. Moreover, TMI explained a lower variance of the three models compared to WHR for all the metabolic outcomes. Therefore, in the effort of select a feasible screening tool for the clinician, WHR might represent a more valid measure compared to TMI and BMI-z score.

P1-355

A comparison of insulin resistance indices: HOMA and Belfiore in 6-8-year-old, properly growing children, born small for gestational age

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Introduction: It is well known that low birth weight in children (born small for gestational age, SGA) predisposes them to the occurrence of obesity, insulin resistance (IR) and lipid disorders, observed even through the whole first decade of life. Thus, early diagnostics and prevention are very important. The HOMA index is used to assess insulin resistance (IRI_{HOMA}). However, in some cases, high, prolonged postprandial insulin secretion is observed despite the low, adequate fasting glucose and fasting insulin levels. This can easily be assessed during the oral glucose tolerance test (OGTT). One of the indicators that properly analyses glucose and insulin levels during OGTT is Belfiore IR index ($\text{IRI}_{\text{Belfiore}}$) in the modification intended for the pediatric population.

The aim of the study was to compare IRI_{HOMA} (which evaluates fasting glucose and insulin) with IRI_{Belfiore} (which evaluates glucose and insulin areas under the curve during OGTT) in children born SGA, being in the prepubertal period, in the first decade of life, in order to determine the usefulness of IRI_{Belfiore} in the diagnosis of children with SGA.

Material and Methods: 126 children born as SGA, aged 6-8 years, with normal height were enrolled in the study. In each child, OGTT was performed after administering 1.75 g/kg of oral glucose. The glucose and insulin serum concentrations were evaluated at 0, 60th and 120th minute of the test. Based on the results, the IRI_{HOMA} and IRI_{Belfiore} were calculated. In addition, the body mass index (BMI), waist to height ratio (WHtR), lipids profile and blood pressure were assessed. IRI_{HOMA} higher than 2.0 and IRI_{Belfiore} higher than 1.27 was considered abnormal.

Results: No elevated IRI_{HOMA} was observed in any of the children, while elevated IRI_{Belfiore} was found in 13 children. The insulin concentration at 0 and 120th minute during OGTT showed a strong positive correlation with each other. What is more, a strong correlation was demonstrated between IRI_{HOMA} as well as IRI_{Belfiore} and: HDL-cholesterol, triglycerides, BMI, WHtR, and blood pressure.

Conclusions: Despite the normal fasting insulin concentration in children with SGA, there is an IR tendency, which can be demonstrated on the basis of OGTT results. In such cases, it seems advisable to use some methods to prevent IR complications already at this stage of children's lives. The result of the IRI_{HOMA} is not a reliable diagnostic tool for children with SGA in the first decade of life.

The medical history revealed that his father had been ill with T2DM for 3 years and had retinopathy and neuropathy. The patient had neonatal muscle hypotonia, feeding problems, delayed development progress during childhood, orchiopexy at 1,5 years and progressive hyperphagia and obesity from 2 years of age. The boy was diagnosed with PWS at the age of 5.

On physical examination the patient had abdominal obesity (87,6 kg, BMI SDS=+3,64) with acanthosis nigricans and characteristic clinical features, such as acromicria, dolichocephaly. The height was 146,9 cm (SDS=-1,8), Tanner stage1.

Laboratory data showed high level of C-peptide 6,28 ng/ml (1,1-4,4), HbA1C-9,9%. The standard liquid meal test showed the preserved C-peptide secretion (max 13,46 ng/ml) and high post-prandial glucose (11,5 mmol/l). Taking in account the presence of diabetes mellitus in obese PWS patient with the clinical features of insulin resistance (acanthosis nigricans) and preserved C-peptide secretion the T2DM was suspected and Metformin therapy was initiated. During the 2-week of Metformin treatment (1500 mg/day) the insulin doses were able to be reduced to 4U/day (only Lispro) and glycemic profile was improved (blood glucose 5-7 mmol/l). To our surprise the IA-2A and ZnT8A levels were positive (32U/ml and 199,4 U/ml, respectively). So, the boy was diagnosed with T1DM. We didn't find the diabetes mellitus complications during examination.

Discussion: To our knowledge this is the first report of combined presentation of features both type 1 and 2 diabetes in PWS, so called «double diabetes». Further long-term evaluation of this patient will show the particularities of the T1DM development in PWS patient with obesity and insulin resistance.

P1-356

The “double diabetes” in adolescent with Prader-Willi syndrome

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Background: Prader-Willi syndrome (PWS) is a complex multisystem disorder that arises from lack of expression of paternally imprinted genes on chromosome 15q11-q13. Its major clinical features include neonatal hypotonia, short stature, developmental delay, hyperphagia, childhood onset obesity, hypothalamic endocrinopathy and characteristic appearance. It is known that due to severe obesity PWS patients are prone to develop type 2 diabetes mellitus (T2DM), while type 1 diabetes mellitus (T1DM) is extremely rare in this syndrome.

Case history: We are reporting on 14 years old boy, who was referred to our department due to uncontrolled glycemic status (blood glucose range 12-15 mmol/l). He was diagnosed to have diabetes mellitus at the age of 13 with classic manifestation (polyuria, polydipsia, fatigue) with ketonuria and hyperglycemia (blood glucose-28 mmol/l, HbA1C-8,1%). The insulin therapy was begun. The boy received mixed insulin therapy (lispro, glargin 27U/day (0,3 U/kg/day).

P1-357

Evaluation of body composition and resting metabolic rate in adolescents with KS

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Background: Klinefelter syndrome (KS) is a frequent anomaly of sex chromosomes, due to the presence of an extra X chromosome (one or more) in the karyotype 46, XY. This disease is characterized by hypergonadotropic hypogonadism and a high risk of developing disorders of carbohydrate and fat metabolism, despite the absence of a pronounced androgen deficiency in adolescents with KS. There are reports of changes in body composition in adolescents with KS even before the symptoms of hypogonadism appear.

Objective: To analyse the body composition and resting metabolic rate (RMR) among adolescents with KS.

Patients and Methods: We examined 20 adolescents with KS, comparable in age and the puberty stage according to Tanner classification. Patients were divided into 2 groups depending on the presence or absence of signs of hypogonadism (reduced level of testosterone, eunuchoid body shape). We investigated the hormonal profile, evaluated the body composition using the Tanita (Japan) body composition analyzer BC-418MA and determined the RMR using the indirect calorimetry method in all children. We used the RMR indicator adjusted for the lean mass (LM) - RMR/LM.

	Number of patients	Age, years	Bone age, years	Puberty stage	Testosterone, nmol/l	SDS BMI	Body fat, %	RMR/LM, kcal/kg
KS with signs of hypogonadism	7	15.32 [15.06;17.79]	14.5 [14.5;16.5]	3 [3;4]	8.66 [3.69;8.98]	0.25 [-0.48;0.83]	16.3 [14.9;19.4]	33.1 [31;34.4]
KS without signs of hypogonadism	13	16.04 [15.11;16.63]	16.5 [15.5;17.0]	4 [3;4]	11.4 [10.4;14.2]	-0.23 [-1.28;0.32]	15.1 [12.7;22.3]	33.3 [29.4;35.5]

Results: 1) Among 20 adolescents with KS 60% (n=12) showed normal resting metabolic rate, 25% showed reduced metabolism (n=5), 15% had increased metabolism (n=3).

2) Normal body composition was detected in 65% of the patients (n=13), excess fat was detected in 25% (n=5), 10% had fat deficiency (n=2).

3) Correlation analysis revealed average positive correlation between the amount of LM and RMR ($r=0.59$, $p <0.05$) and a strong positive correlation with SDS BMI ($r=0.78$, $p <0.05$).

4) The correlation analysis of the RMR/LM did not reveal its connection with blood testosterone levels.

5) Comparative analysis of two groups of patients with KS revealed no differences in terms of RMR/LM.

Conclusions: Most patients with KS in our study revealed normal indices of body composition and RMR regardless of the level of testosterone. No correlation between the basal metabolism and the level of testosterone may indicate a slight effect of androgen deficiency on energy metabolism at rest in adolescents with KS.

Material and Methods: A retrospective observational study was conducted on a sample of 213 children, age 5-18 years, divided in two groups according to body mass index (BMI) standard deviation scores (SDS): a group with overweight/obesity (BMI >1 SDS) and a normal weight group ($-1 < \text{BMI} < 1$ SDS) who were evaluated in the Endocrinology Department of the Mures County Hospital. Demographic data, body composition (bioimpedance analysis), metabolic profile (glucose, insulin, lipids, uric acids), and RBP4 level were evaluated in every subject. Additionally, 2 SNP of the RBP4 gene were analyzed (rs3758539 and rs10882280). The study was approved by the local ethics committee and all subjects and legal representatives signed an informed consent. Statistical analysis used SPSS v. 25 with a level of significance $\alpha=0.05$.

Results: 130 overweight and obese and 83 age and sex matched normal weight children were included. None of the SNPs are associated with obesity, even after adjusting for sex. Levels of RBP4 negatively correlate with glucose levels ($r= -0.178$, $p=0.022$), but not after adjusting for age and sex. Body composition, metabolic profile and anthropometric parameters differ significantly between study groups. There were not statistically significant differences between groups regarding the RBP4 levels, albeit we found higher level in the obese group (13.1 vs 11.8 $\mu\text{g}/\text{ml}$, $p=0.194$).

Conclusions: RBP4 gene polymorphisms rs3758539 and rs10882280 are not associated with obesity in Romanian children. RBP 4 level is higher in obese children and correlates only with glucose levels.

Keywords: RBP4, obesity, children, SNP, Romania

P1-358

Relationship between RBP4 level and two of its gene polymorphisms with body composition and metabolic profile in obese children

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Background: The role of retinol binding protein 4 (RBP4) in the insulin resistance associated with obesity is still unclear and various studies have analyzed the role of its gene polymorphisms as a potential key to understanding the mechanisms involved.

Aim: The current study aimed to analyze the relationship between RBP4 levels, the distribution of two SNP (rs3758539 and rs10882280) and the metabolic, anthropometric parameters and body composition in obese vs. normal weight children.

GH and IGFs

P1-359

Insulin-like growth factor 2 in pediatric gliomas: expression, intracellular localization and association with clinical outcome

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Background and Aim: Gliomas are the most frequent solid tumors in pediatric population. The IGF system of ligands and receptors are known to play an important role in both normal and neoplastic growth. In a previous work we have reported the quantitation of some components of the IGFs system in SNC pediatric tumours (IGF-1, IGF-2, IGF-1R, IR), being IGF-2 expression the most variable among all the genes studied.

Our aim was to characterize the expression and intracellular localization of IGF-2 in pediatric gliomas, and its association with clinical outcome.

Methods: We performed a prospective study (6/2012-01/2017) of pediatric patients with gliomas without previous medical treatment that underwent surgery in our Hospital. Tissues were collected at the time of surgery. IGF-2 intracellular localization was assessed by Immunohistochemistry in fixed tumor samples and gene expression was measured by qPCR in those where fresh sample were available. IHC for IGF-2 was classified as negative or positive, cytoplasmatic or cytoplasmatic/nuclear staining. Follow up was carried out in collaboration with the Oncology service. Patients were categorized by their clinical outcome as dead, alive with or without tumor. Mann-Whitney, Kruskal-Wallis followed by Dunn's Test were used for comparisons.

Results: We performed IHC for IGF-2 in 96 samples from pediatric gliomas (low grade n=80 and high-grade n=16) and found IGF-2 negative staining in 10 samples, 19 samples with cytoplasmatic and 67 samples with cytoplasmatic and nuclear staining. No association was found between IGF-2 cellular localization and tumor grade, nor with clinical outcome.

Fresh samples from 34 patients with low (n= 27) and high (n= 7) grade gliomas, 15 M/ 19 F, and a median age of 7.41 years (range 0.96 – 14.65) were processed for IGF-2 gene expression quantitation. IGF-2 mRNA levels were detected in all samples studied. When analyzed by follow up (median 5.34 years; range 2.35 – 6.84), IGF-2 expression was higher in living patients bearing tumors compared to tumor free or deceased patients, regardless of tumor grade. This association persisted in low grade tumors while was not found in patient with high grade gliomas.

Conclusions: In contrast with results found in other tumors, IGF-2 intracellular localization performed by IHC does not correlate with clinical outcome in pediatric gliomas. In low grade gliomas the association of initial elevated IGF-2 mRNA levels with clinical outcome suggest a role for IGF2 in the biological behavior of these tumors and could be a valuable prognosis marker.

P1-360

Prevalence of children born small for gestational age with short stature who qualify for growth hormone treatment: a preliminary population-based study

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Background: In 2003 recombinant human growth hormone (rhGH) was approved by European Medicines Agency to treat short children born small for gestational age (SGA), but so far no study evaluated the prevalence of SGA children with short stature who qualify for rhGH treatment in Europe.

Objectives: To investigate the prevalence of SGA and short stature in children born SGA and of SGA children who qualify for rhGH treatment at 4 years of age in an Italian population.

Methods: A preliminary population-based study on 6 (out of 20) primary care pediatricians' databases was conducted in Trieste, Italy. We collected data on 3,595 children who were born between 2004 and 2014 (over 20,120) and who had 4 years of follow-up. Birth weight (BW) or birth length (BL) SDS for sex, gestational age (GA) and birth order (BO) were calculated according to Bertino Italian charts through web-based calculator (www.inescharts.it) and SGA was defined as BW and/or BL \leq -2 SDS. Data on height and weight were collected at the closest visit to 1, 2, 3 and 4 years of age and SDS were calculated by Growth Calculator version 3 (www.weboriented.it/ghc3/). Short stature was defined as height \leq -2 SDS according to WHO charts for children <5 years. In Italy, short children born SGA can start rhGH treatment when fulfilling all the following criteria: BW or BL \leq -2 SDS for sex and GA according to Bertino charts, age \geq 4 years, height \leq -2.5 SDS, growth velocity $<$ 50° percentile.

Results: Full data at birth were available for 3,136 children. The prevalence of SGA was 3.6%: 0.8% SGA for weight; 2.2% SGA for length, 0.6% for both weight and length. The prevalence of short stature among SGA children was 9% at 1 year, 6% at 2 years, 4% at 3 years and 3% at 4 years of age. Only 1 child born SGA was eligible for GH treatment: she was not referred to endocrinologist.

Conclusions: Although the prevalence of SGA in our population is similar to previous studies, data on catch-up growth are different from previous reports by Karlberg. Moreover 40% of short children at the age of 2 years in our cohort improved their height later. The prevalence of children born SGA who qualify for GH treatment was 1:3,136, much smaller than the prevalence of 1:1,800 reported by Fujita in the only similar study conducted in Japan (with evaluation at 3 years).

P1-361

Long-term Safety of a once-weekly Somatropin (hGH-CTP): 4-Year Results of a Phase 2 Extension Study in Children with Growth Hormone Deficiency

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Background: Once-daily growth hormone (GH) therapy is an effective treatment for children with growth hormone deficiency (GHD), but compliance wanes with ongoing treatment. A once -weekly GH, somatropin (hGH-CTP), is being developed to reduce the treatment burden of daily dosing for children and caregivers and potentially improve compliance and long-term efficacy. The impact of once-weekly somatropin on long-term safety, local tolerability and immunogenicity was assessed in patients treated with somatropin for a period of up to 4 years in an open-label extension (OLE) of the somatropin Phase 2 study.

Objective: To evaluate the safety, local tolerability and immunogenicity of long-term exposure to somatropin in GHD children.

Design: A multicenter, open-label, controlled extension of a Phase 2 trial in children with GHD (ClinicalTrials.gov: NCT01592500).

Methods: Forty-eight GH-treatment-naïve prepubertal children with GHD that completed 12-months of treatment in the main Phase 2 study continued in the OLE. All eligible subjects were treated at the 0.66 mg/kg/wk dose after the first year of the extension study.

Results: Data from the 12-month Phase 2 study showed comparable height velocity and insulin-like growth factor-1 (IGF-1) values in weekly somatropin-treated compared to daily Genotropin-treated subjects. In the OLE portion of the study, there were 214 AEs occurring in 44 subjects (91.7%). One subject was discontinued because of an SAE of exacerbation of thoracic scoliosis. The majority of AEs (68.8%) were mild in nature and were deemed not related to somatropin. The most frequent AEs were upper respiratory infections (31.3%), rhinitis (18.8%) and bronchitis (10.4%). Twelve AEs (3%) related to somatropin were of a similar nature and severity as reported for daily r-hGH products. Somatropin treatment showed that IGF-1 and IGF-binding peptide-3 (IGFBP-3) levels were maintained within the normal range with ongoing somatropin therapy. Low titers of anti-somatropin antibodies were detected in 16 subjects but no neutralizing anti-somatropin antibodies were identified. The growth rate remained within expected range in all subjects. Thirty-eight subjects (79%) are continuing in the fifth year of the OLE.

Conclusion: Somatropin treatment demonstrated a favorable safety profile and local tolerability after four years of dosing in GHD pediatric subjects. The safety and tolerability from the OLE study were comparable to that observed in the 12-month main

Phase 2 study and the reported safety profile of daily r-hGH. Serum IGF-1 SDS values were maintained within the normal range, and a growth rate comparable to that reported for daily hGH was observed.

P1-362

Sequencing Approach to identify candidate genes involved in short stature

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Background/Aims: Short stature is a common reason for presentation to paediatric endocrinology clinics. Getting to a diagnosis of short stature is a multi-step, complex process of tests that only in a few cases save a diagnosis. As genetic plays a strong role in height, we sought to identify known and novel genetic causes of short stature.

Methods: We recruited 18 children with severe short stature, we conducted whole exome sequencing (WES) on trio (both parents and their affected child) to detect *de novo*, homozygous and compound heterozygous variants; our aim was to extend the identification of the genetic bases of short stature by searching for known and novel candidate genes/pathways. We used an analysis pipeline to identify both rare and polymorphic genetic variants that cause the short stature.

Results: Clinical exome sequencing was performed on 18 patients with suspected genetic conditions of short stature, belonging to 11 families and was extended on their parents. We identified a known genetic disease cause in 7/18 patients, corresponding to a molecular diagnostic rate of 39%. These included cases of: i) Hypochondroplasia, ii) Hypoparathyroidism-retardation-dysmorphism syndrome, iii) Microcephalic osteodysplastic primordial dwarfism, type II, iv) Isolated growth hormone deficiency due to defect in GHRH, v) Hypothyroidism central, vi) Partial growth hormone deficiency, vii) 1 case of delayed puberty, in which we have found mutation in *IGSF10* gene. For the remaining patients (11/18 patients), we have generated lists of candidate variants. In the most patients with growth hormone deficiency, we identified a polymorphic intronic variant, that influences GH1 mRNA expression and secretion, together with other polymorphic or rare variant/s in other genes responsible to GH secretion. These finding highlights that despite the diagnosis in some patients is evident, the identification of genetic cause is very complicate: it's necessary evaluate the contribution of more variants also in genes not yet characterized.

Conclusions: These finding could be helpful for identifying causal functional variants and increasing our basic knowledge; our results highlight that WES provide new insights useful for the genetic diagnosis of short stature, as well as for the identification of biological pathways that will be potentially targeted by new therapeutic strategies. Additionally, the understanding of genetic bases of short stature phenotype will be useful to direct treatment decisions surrounding use of growth hormone or insulin-like growth factor 1 therapy.

P1-363

Metabolism of somapacitan, a long-acting growth hormone derivative, in human subjects

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Background: Somapacitan is a reversible albumin-binding growth hormone (GH) derivative developed for once-weekly administration in patients with GH deficiency (GHD). It consists of a human GH backbone, similar to endogenous human GH, with one amino acid substitution, attached to an albumin binder via a linker chain.

Objective: Absorption, metabolism and excretion (AME) of somapacitan were investigated in a Phase 1 trial (NCT02962440). Absorption and excretion data have been reported previously. Here we report on the metabolic fate of somapacitan, its linker chain and albumin binder.

Methods: Metabolites were identified and quantified in plasma and urine collected from seven healthy males aged 45–62 years, following a single administration of 6 mg somapacitan containing 20 MBq [³H]-somapacitan radiolabel. The pharmacokinetics (C_{max} and AUC) of the plasma components were determined and the radioactive peaks of the most abundant plasma metabolites (>10% of total AUC of the somapacitan-related material) and urine metabolites were selected for HPLC fractionation with reversed phase chromatography and UPLC-mass spectrometry (MS) analysis. Fractions with individual plasma and urine components were analysed with liquid chromatography-MS and liquid chromatography-radioactivity monitoring for structure identification.

Results: Three abundant plasma metabolites (P1, M1 and M1B) and two abundant urine metabolites (M4 and M5) were identified. In plasma samples, somapacitan was the principal component up to 168 hours after dosing. P1, M1 and M1B were the most abundant and the only plasma components at 336 and 504 hours. The AUC of intact somapacitan accounted for 59% of the total AUC of all somapacitan-related material, P1 accounted for 21%, and M1 plus M1B accounted for 12%. M4 and M5 were the most abundant urine metabolites and accounted for 37% and 8%, respectively, of the administered somapacitan radioactivity. M1, M1B, M4 and M5 were identified as metabolites formed after extensive degradation of the peptide backbone of somapacitan, leaving a tetrapeptide attached to the linker and albumin binder (M1). Deamidation of

asparagine to aspartate in M1 forms M1B and further degradation of M1 or M1B forms M5 and M4. P1 was not structurally identified, but is likely to be identical to M4 or a conjugate thereof. No intact somapacitan was found in excreta, suggesting full degradation of somapacitan prior to excretion of small residual fragments.

Conclusion: These data describe the metabolic fate of somapacitan, its linker chain and albumin binder in human subjects, and demonstrate that somapacitan is extensively degraded prior to excretion of small residual fragments.

P1-364

GH Values In Serum And Blood Spots On Filter Paper Samples In Neonates Until 30 Days Of Life By Electrochemiluminescence (ECLIA)

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Growth Hormone deficiency (GHD) in newborn is an infrequent condition, which can cause threat to life due mainly to hypoglycemia that begins in the first week of life. A GH basal level (whether random or associated with spontaneous hypoglycemia) that distinguishes infants with GHD from those with GH sufficiency in the neonatal period is not conclusive. Few data have been reported about the GH measurements in serum and dried blood spots on filter paper samples in healthy neonates.

Aims: To compare and correlate the GH values in serum and blood spots on filter paper samples in neonates until 30 days of life. To establish GH reference values in healthy newborn until 15 days of life. To analyze the correlation between GH concentrations in serum and whole blood spot and with hormones of the hypothalamic-pituitary-gonadal and adrenal axis. Subjects and methods: We analyzed 281 serum and whole blood spots samples obtained from AGA neonates between 2-30 days of life (2-5 days n=147, 6-15 days n=69, 16-30 days n=65) (F: 144, M: 137). GH concentrations (ng/mL) were measured by ECLIA Roche C600 (IRP 98/574) in serum as well as eluted from filter paper samples. The mean and SD GH value, P 5.0 and P 95.0 were calculated. Spearman correlation coefficient was used.

Results: Serum mean GH and (SD): **2-5 days:** 20.81(15.8); P5: 6.30, P95: 42.30; **6-15 days:** 8.78 (4.34); P5: 3.29, P95: 15.19 and **16-30 days:** mean GH: F: 10.55 (4.58), M: 7.72 (3.75). **Blood spots** mean GH and (SD): **2-5 days:** 17.58 (9.95); P5: 5.68, P95: 33.60; **6-15 days:** 10.31 (5.88), P5: 3.0, P95: 21.02 and **16-30 days:** mean GH: F: 10.41 (6.01), M: 10.99 (7.78). The Spearman correlation obtained between both techniques in parallel measurements was $r^2=0.85$ ($p<0.0001$).

Conclusions: Our results showed high average GH levels in the first few days of life. Newborn screening card spotted with blood during the first week of life provides such high levels that, even at the nadir of GH pulsatility a basal value could contribute to detect GHD accurately. The good correlation obtained between both types of samples would indicate that the measurement of GH

in dried blood spot samples is an appropriate and reliable method which can be incorporated in the diagnosis of neonatal GHD. The newborn screening samples may be a valuable resource for retrospectively assessing GH sufficiency if this neonatal window has passed.

P1-365**De novo formation of neutralizing IGF-I antibodies during rhIGF-1 treatment in a girl with IGFALS deficiency as distinct adverse event interfering with growth promotion**

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Background: IGFALS deficiency is a rare cause of GH insensitivity (GHI). We report a German girl with short stature who was born as 2nd child at 40 weeks of gestation. Her Caucasian parents were unrelated and healthy (target height 168 cm, SDS 0.2). She was born appropriately sized for gestational age (49 cm, SDS -1.2; 2950 g, SDS-1.2). Height (104.8 cm; SDS -2.94) and height velocity (5.1 cm / year; SDS -1.67) were reduced at the age of 6 years.

Methods/Patient: Serum concentrations of total IGF-I (SDS -2.3; RIA, Mediagnost, FRG), of IGFBP3 (SDS -7.7) and of stimulated GH (max. 7.69 ng/ml) were reduced. cMRT was normal. Height (SDS -3.31), height velocity (SDS -1.68) and serum concentrations of IGF-I (SDS -2.5) and IGF BP 3 (SDS-9.1) remained low during growth hormone therapy (rhGH) for 18 months. Spontaneous GH secretion was elevated (12 hours sampling every 20 minutes: mean GH concentration 7.2 ng/ml, reference >3; 24h area over 0-line 174.79 ng/mlx24 h, reference > 80). ALS serum concentration was low (102 mU/ml; reference 705-1270).

A novel compound heterozygous mutation of the IGFALS gene (chromosome 16; Exon 2) was found: *IGFALS p.Pro474Leu/p.Phe602Cys*.

Treatment Course: Therapy with rhIGF-I was started with 2x40µg/kg/d and gradually escalated to 2x120µg/kg/d s.c. Headaches without papilledema, dizziness and leg pain were reported during follow up. Sequential sampling revealed persistent elevated serum concentrations of IGF-I before (SDS 2.7) and after (SDS 5.61) rhIGF-I injections. Serum glucose and potassium were within the reference ranges throughout. Treatment was stopped after 10 months as no catch up growth occurred (Δ HSDS -0.26; HV SDS -0.94). Serum samples were also screened for anti-rhIGF-I antibodies by electrochemiluminescence assay (ECLA) which revealed low antibody titres before (<1:20) and after treatment (<1:100) but significantly elevated titres during the treatment period (max. 1:2048). Screening for auto-immune diseases remained negative.

Discussion: IGFALS deficiency is a rare cause of GHI. Neither rhGH nor rhIGF-I stimulated growth of our patient. Severe adverse events and lack of efficacy prompted to stop rhIGF treatment. In addition to elevated total IGF-I, neutralizing anti-rhIGF-I antibodies were detected in serum during rhIGF treatment but neither

before start of treatment nor after withdrawal. The aetiology of the formation of anti-rhIGF-I antibodies in this patient with IGFALS deficiency during rhIGF-I treatment remains obscure. We speculate that the immunogenic potency of circulating IGF-I exceeds that of local tissue IGF-I.

P1-366**Glomerular filtration rate in young adults born SGA: a 5-year longitudinal study after cessation of GH treatment**

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Background: GH treatment increases glomerular filtration rate (GFR), as serum IGF-I stimulates the renin-angiotensin system. Data on longitudinal changes in GFR after cessation of GH treatment in young adults born small for gestational age (SGA) are not available. It is essential to ascertain longitudinal data after cessation of GH treatment, to evaluate the possible long-term effects of higher serum IGF-I levels during childhood treatment on adult GFR.

Method: Longitudinal study in 230 young adults born SGA, previously treated with GH (SGA-GH). Serum creatinine levels were determined at cessation of GH treatment and at 6 months, 2 and 5 years thereafter. Data at 5 years after cessation of GH were compared with untreated age-matched controls (untreated short subjects born SGA (SGA-S), subjects born SGA with spontaneous catch-up growth (SGA-CU), subjects born appropriate for gestational age (AGA)).

Results: After correction for age, GFR decreased significantly during the first 6 months after cessation of GH treatment, while remaining well within the normal range (124.6 vs. 120.2mL/min/1.73m², p<0.001). GFR did not change between 2- and 5 years. GFR at 5 years after GH cessation was compared to that of 56 age-matched SGA-S, 118 SGA-CU and 135 AGA young adults. SGA-GH adults had a similar GFR as the untreated SGA-S and AGA adults, but GFR was lower compared to SGA-CU (108.7 vs. 119.6 mL/min/1.73m², resp., p=0.02).

Conclusion: In conclusion, our 5 years longitudinal follow-up study shows a decrease in GFR during 6 months after GH cessation, but GFR remained stable and within the normal range. GFR at 21 years of age was similar in GH-treated young adults born SGA and the untreated SGA-S and AGA young adults. We, therefore, conclude that long-term GH treatment in children born SGA has no unfavourable effects on kidney function in early adulthood.

P1-367**Normal IGF-bioactivity and low free IGF-I in patients with Prader-Willi syndrome with high total serum IGF-I: immunoreactive IGF-I concentration poorly reflects IGF bio-activity and bio-availability**

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Introduction: Recombinant Growth Hormone (GH) has changed the lives of many patients with Prader-Willi Syndrome (PWS). GH treatment has beneficial effects on body composition, physical performance, cognition, psychomotor development, respiratory function and quality of life of patients with PWS. Due to the narrow therapeutic range, GH treatment is subject to strict limits. Clinicians measure serum immunoreactive Insulin-like Growth Factor 1 ('total IGF-I') levels to titrate the dose of GH. However, in patients with PWS, IGF-I levels are often much higher than expected based on GH dose. As a result, clinicians have to reduce the GH dose, with consequent loss of beneficial effects. Based on our previous data (Bakker et al, JCEM 2017) and the observation that patients with PWS seem to benefit from relatively high GH doses, we hypothesize that IGF might be less active, or less available, in PWS. Low IGF bioactivity or bio-availability would imply that high total IGF-I levels might not have negative side effects in patients with PWS. In that case, GH dose reduction might not be needed.

Methods: We measured total IGF-I, bioactive IGF and free 'bio-available' IGF in 22 PWS patients and 112 healthy controls. IGF-I bioavailability ('free IGF-I') was measured by commercially available ELISA (Ansh Labs, Webster, TX). IGF-bioactivity was measured by an in-house IGF-I receptor kinase activation assay (KIRA), a cell-based system where IGF bioactivity is reflected by phosphorylation of the IGF receptor. Both IGF-I bioavailability and IGF-bioactivity were compared with total (immunoreactive) IGF-I values.

Results: We found a striking difference in free IGF-I between PWS and control samples. Free IGF-I correlated poorly to total IGF-1 levels. Correlation between IGF-bioactivity and total IGF-1 was also very low. Most importantly, PWS patients with high immunoreactive IGF-I during GH treatment showed normal IGF-bioactivity.

Conclusion: Our results indicate that total IGF-I is a poor marker of IGF-bioactivity in PWS patients, as IGF-bioactivity in PWS patients with high total IGF-I concentrations was comparable to IGF-bioactivity in controls. It suggests that clinicians might not need to lower GH dose in patients with a high total IGF-I. Further studies are needed to confirm our data and find more reliable parameters for GH dose titration in PWS.

P1-368**Renal Complication of Hematuria and Proteinuria after Recombinant Human Growth Hormone Therapy in Children**

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Introduction: Treatment with recombinant human growth hormone (rhGH) is useful for growth failure in short stature children. But there are some reports of renal disease or complication occurring during rhGH treatment. GH and insulin-like growth factor-1 (IGF-1), together with other growth factors and cytokines, have important roles in adaptive morphological and functional changes in the kidney. This study was aimed to reveal the renal complication of hematuria and proteinuria in children and adolescents those who have received rhGH treatment.

Methods: We retrospectively reviewed the medical records of children who treated with rhGH. Enrolled patients were divided into five groups according to the underlying disease; growth hormone deficiency (GHD), idiopathic short stature (ISS), small for gestational age (SGA), short stature with central precocious puberty (CPP), and Turner syndrome (TS).

Results: 169 patients (76 males, 93 females) were enrolled and the mean age was 9.8 (± 3.0) years. 53 patients (31.4%) were GHD, 17 (10.1%) were ISS, 30 (17.8%) were SGA, 44 (26.0%) were CPP, and 25 (14.8%) were TS, respectively. 19 patients (14.3%) showed microscopic hematuria or proteinuria. 11 patients (6.5%) had isolated microscopic hematuria, 10 patients (5.9%) showed isolated proteinuria, and two patients (1.6%) had both microscopic hematuria and proteinuria. Renal complication according to the disease was as follows; four out of 53 patients (7.5%) in GHD, two out of 17 (11.8%) in ISS, three out of 30 (10.0%) in SGA, two out of 44 (4.5%) in CPP, and eight out of 25 (32.0%) in TS, respectively.

Conclusions: In our study, 19 patients (14.3%) who underwent rhGH therapy showed renal complication such as microscopic hematuria and/or proteinuria. In patients with TS, eight (32.0%) out of 25 patients revealed renal complication. We must carefully follow up for any renal complication in those who have received rhGH treatment, especially in Turner syndrome.

P1-369**Detection and referral of children with short stature in Serbia - the impact of electronic growth charts**

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Introduction: in countries with highly developed health information systems (HIS), early detection of short stature (SS) is facilitated by automated anthropometric calculations, with warning alarms and automated referrals when prespecified conditions are met (poor growth velocity etc.). In countries where available HIS resources are insufficient for implementation of complex automated systems for growth supervision, much simpler, graphical-based growth electronic charts can be implemented in order to assist physicians in detection of growth disorders just by displaying growth charts in patient electronic health records. Such electronic growth charts (EGC) were implemented in Serbia during the year 2015.

Objective: to determine if the introduction of EGC in health-care system of Serbia resulted in changes regarding the age of referral and number of referred children, gender and aetiology of SS in patients referred to tertiary centre for endocrine evaluation of SS.

Method: data were collected from the medical records of the Department of Endocrinology of the Mother and Child Healthcare Institute of Serbia „Dr Vukan Cupic“. Records of 664 children referred to our hospital were analysed – first group (n=293) consisted of all children referred during two years prior to the implementation of EGC in Serbia (Period 1 - from January 1st 2013 to December 31st 2014), and the second group (n=371) was comprised of all children referred to our centre after the EGC implementation (Period 2 - January 1st 2016. - December 31st 2017). Epidemiological data, as well as final diagnoses regarding aetiology of the SS were collected for all subjects.

Results: analyses showed that the number of patients referred for evaluation of SS increased significantly from Period 1 to Period 2 (293 to 371, p=0,002). Also, after EGC implementation, less children with normal familial, physiological variants of SS were referred for endocrine evaluation compared to Period 1 (7.8% vs. 17.1%, p<0,001), and consequently the percentage of children with pathological causes of SS such as growth hormone deficiency increased (from 37.5% to 42.3%, p<0,001). No statistically significant changes were observed regarding the gender of patients and age at the time of referral.

Conclusion: presented data indicate that in countries where e-Health resources are limited and where implementation of complex automated systems for growth supervision cannot be introduced, even simple graphic growth e-charts like EGC introduced in Serbia in 2015 can result in higher number of referrals for the evaluation of SS, while also decreasing unnecessary referrals of children with physiologic causes of SS.

P1-370**Challenges experienced in delivering growth hormone therapy in children's with Prader Willi syndrome in Birmingham Children's Hospital**

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Prader Willi Syndrome (PWS) is a rare neuro-genetic disorder inherited as a result of lack of expression in 15q11-13 gene and 70% are paternally inherited. Characteristic features are dysmorphism, behavioural problems, infantile hypotonia, short stature, hypothalamic dysfunction, hyperphagia and morbid obesity. The long-term morbidity and mortality depend on hypothalamic dysfunction and obesity. While multidisciplinary care is essential, growth hormone (GH) is a recognized treatment modality to improve body composition.

The objective of this retrospective audit was to analyse the efficacy of GH therapy on PWS patients at Birmingham Children's Hospital.

Current guidelines recommend a starting dose of 9–12mcg/kg/day whilst aiming to gradually increase to 35mcg/kg/day within a few months, while maintaining IGF-1 level below +2SDS.

Out of 37 PWS patients 29 had received GH. Among GH-treated group, 21 patients had either scoliosis or obstructive sleep apnoea (OSA); only one had received a subtherapeutic starting dose.

During follow up, 18 patients had IGF1 above +2SD at some point with subsequent reduction in dose. Out of the 11 patients who had normal IGF1, 5 received less than 22mcg/kg/day due to the presence of scoliosis or OSA, one had only recently started, and 5 patients were treated with GH 28–35mcg/kg/day.

Therapeutic and sub-therapeutic doses of GH-treated groups were compared with independent sample T test. In both groups, height standard deviation score (SDS) had decreased (-1.33, -2.22 respectively) significantly (p values 0.014 and 0.000 respectively). In the sub-therapeutic group, weight and body mass index (BMI) mean SDS were increased by 0.563 and 0.490 respectively. In the therapeutic dose group, weight SDS mean was increased by 0.0413 and BMI SDS mean was decreased by 0.0534. However, BMI and weight changes were not statistically significant. Furthermore, out of the 5 patients who received recommended doses of GH three were treated for less than 30 months and the duration may not be enough to demonstrate a significant effect.

In conclusion, high IGF1 was a limiting factor for optimum delivery of GH in PWS patients. However, the number of patients and duration of treatment were not adequate to demonstrate significant effect of GH in the adequately-treated group.

There is evidence in other studies, that PWS patients tend to have significantly high IGF1 levels with GH therapy. Therefore, further multi-centered studies conducted for over longer periods are needed to evaluate whether GH significantly increases either the bioavailability of IGF1 or GH-related adverse effects in PWS.

Growth and Syndromes (to Include Turner Syndrome)

P1-371

Growth Hormone Deficiency (GHD): Assessing Parent Burden for Child Growth Hormone Deficiency Treatment: the Growth Hormone Deficiency - Parent Treatment Burden Measure (GHD-PTB)

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Background: Treatment for child GHD requires daily injections, which can be painful and disruptive. For most children, these injections are administered by an adult, usually their parent. Unfortunately, little is known about the burden that a child's treatment places on a parent. The GHD-PTB was developed according to FDA/EMA guidances to address this gap. Items were based on qualitative interviews of 31 parents of children with GHD, ages 4 to <13 years. This study presents the GHD-PTB psychometric validation results.

Methods: A non-interventional, multi-clinic-based study (US/UK) of pre-pubertal children with GHD and parents/guardians of similar children was conducted. Psychometric analyses were completed according to an a-priori statistical analysis plan to determine the measurement model, reliability, validity, responsiveness, and minimally important difference (MID).

Results: The analytic data included 98 parents (mean age children 9.2 years and parents 41.6 years) who were predominantly mothers (80.7%), married (88.1%), and worked (51.0%). Item reduction resulted in an 8-item measure. Factor analyses identified 2 domains: Interference in Daily Life and Emotional Well-being. For each domain and the Overall score, internal consistency reliability was acceptable (Cronbach's alpha >0.70) as was test-retest for Emotional and Overall (>0.70) and slightly lower than expected for Interference (0.60). Convergent validity hypotheses for domains and Overall were proven ($p<0.01$, $r>0.40$). Known groups validity hypotheses were proven for Emotional, which discriminated between whether the parent gave the injections more often than the child ($p<0.05$) and the Overall ($p=0.05$). The length of time their child was on treatment did not discriminate suggesting that treatment continues to be interfering over time. Marked improvements after 12 weeks of treatment were noted for Emotional and Overall (16.6 and 8.6 points). The Interference domain score had a very small improvement. Associated effect sizes were -0.74 (Emotional) and -0.69 (Overall), indicating that the GHD-PTB is sensitive to change at high levels. Preliminary recommendation for the MID is 7 points for the Overall, and 10 for Emotional Well-Being and 6 for the Interference domains.

Conclusions: The GHD-PTB was found to be reliable and valid and is considered ready for inclusion in clinical trials and clinical practice. Since parents are often primarily responsible for administering and ensuring compliance of treatment for young

children, accurate and reliable assessment of their treatment burden can help researchers and clinicians better assess the broader range of treatment impacts. Less frequent treatment requirements may reduce this burden for parents.

P1-372

A considerable role of NPR2 mutation in idiopathic short stature: identification of two novel mutations

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Introduction: C-type natriuretic peptide (CNP, *NPPC* gene) and its receptor, natriuretic peptide receptor B (NPR-B, *NPR2* gene), is critical for endochondral ossification in growth plate. Biallelic *NPR2* mutations are known as acromesomelic dysplasia, type Maroteaux which is characterized by severe short stature. A monoallelic *NPR2* mutation has been suggested to mildly impair long bone growth.

Objective: The purpose of this study was to identify *NPR2* mutation in Korean patients with idiopathic short stature (ISS).

Subjects and Methods: One hundred sixteen subjects (60 males) with non-syndromic ISS from Hallym Medical Center and Korea Medical Center were enrolled. *NPPC* and *NPR2* genes were sequenced and the identified variant was filtered with reference dbSNP and COSMIC database. In silico prediction and in vitro functional analysis using cell-based assay were performed to confirm their protein derangement.

Results: Mean age at ISS diagnosis was 8.0 years and mean (with 95% C.I.) height z-score was -2.65 (-2.72 ~ -2.57). Sixty-two percent (72/116) of subjects had delayed bone ages more than one year compared to their chronological ages. Three pathogenic mutants (R921Q, R495C, Y598N) and one benign variant (R787W) of *NPR2* gene was identified and no novel sequence variant in *NPPC* gene was found in all ISS subjects. Two novel pathogenic mutants (R495C and Y598N) were suggested to be highly pathogenic by Mutation Taster and PolyPhen-2 prediction models. cGMP productions after stimulation with CNP decreased significantly in two novel mutants (R495C and Y598N) expressed constructs-transfected cells compared to those of wild type (WT) NPR-B constructs-transfected cells. When cells cotransfected with mutant and WT NPR-B constructs (1:1), they also showed decreased cGMP production compared to empty vector and WT NPR-B constructs-transfected cells.

Conclusions: Heterozygous *NPR2* mutations were found in 2.6% of ISS Korean subjects. This prevalence and a dominant-negative effect of mutant NPR-B on growth signals imply that it is definitely one of genetic causes of ISS.

P1-373**Matrix metalloproteinases, their inhibitors and neurotrophic factors as indicators of cardiometabolic risk in Turner syndrome girls**

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Context: Turner syndrome (TS) predisposes to obesity and related disorders being a part of the metabolic syndrome. As TS population is at a higher risk of cardiovascular diseases research for laboratory markers of metabolic complications is ongoing. Based on our previous observation special significance is attributed to MMPs (matrix metalloproteinases), their inhibitors TIMPs and neurotrophic factors, such as BDNF (Brain-Derived Neurotrophic Factor) and GDNF (Glial Cell-line Derived Neurotrophic Factor).

Objective: The assessment of the correlation between components of metabolic syndrome and selected metabolic markers in girls with TS.

Method: In 17 girls with TS treated with recombinant growth hormone, of whom 9 started puberty (Tanner≥B2), the waist and hip circumferences were measured and the body mass composition was evaluated using the electrical bioimpedance method (BIA). The concentrations of lipid-carbohydrate parameters (T-Chol, HDL-chol and TG; glucose and insulin in OGTT) as well as the concentration of circulating MMP-1, -2, -9, TIMP-1, BDNF, GDNF and VEGF (Vascular Endothelial Growth Factors) were assessed.

Results: Study patients were at the mean age of 11.4±3.9 years with Z-Score BMI -0.08±0.8 and hSDS -2.6±1.0. Regression analysis revealed negative correlation between the level of HDL-chol and following metabolic markers: TIMP-1 ($r = -0.6$; $p = 0.03$), MMP-9 ($r = -0.7$; $p < 0.01$) and BDNF ($r = -0.7$; $p < 0.01$). Total Body Water and Fat Free Mass positively correlated with MMP-9 ($r = 0.6$, $p = 0.03$; $r = 0.6$, $p = 0.04$, respectively). Correlations between other components of metabolic syndrome and metabolic markers were not significant ($p > 0.05$). Puberty resulted in significantly higher fasting glucose and insulin ($p = 0.03$, $p < 0.01$, resp.), but not in differences in metabolic markers ($p > 0.05$).

Conclusion: Our pilot study indicate that MMP-9, TIMP-1 and BDNF could be useful as a potential indicators of cardiometabolic risk complications in TS girls. As estrogens act advantageously on the HDL level, the concentration of mentioned metabolic markers need further study in which the influence of estrogens should be taken into consideration.

P1-374**Growth in the first ten years after Antiretroviral Therapy initiation among HIV-infected children in the CoRISpe spanish pediatric cohort**

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Objectives: Previous studies have described impaired growth in HIV-infected children. Many of them showed weight and height improve after ART initiation. Most series include children from resource limited settings in which malnutrition is frequent and treatment is not fully available. We aim to characterize long-term growth in a cohort of HIV-infected children after ART initiation and to identify determinant factors.

Methods: HIV-infected children born between January 2000 and December 2017 participating in the Spanish Cohort of HIV-infected Children (CoRISpe) with available anthropometric data were included. Clinical and immunovirological variables and anthropometrics were collected yearly during the study period.

Results: A total of 124 children were included, 60.5% female, all vertically HIV-infected and on treatment, 34% born abroad. A 55% of cases were diagnosed immediately after birth, and 53% achieved viral suppression within one year of treatment. Median CD4 cell counts at diagnosis: 1400 cell/mL [400-1800]. Seven patients (5%) were late diagnosis (<200 CD4). At baseline, median Z-score for weight, height and BMI were -1.19 [-1.7 to -0.29], -1.1 [-1.93 to -0.03], and -0.72 [-1.31 to -0.04] respectively. We observed an increase in weight gain and linear growth rate after one year (median z-score for weight, height and BMI: -0.65 [-1.13 to 0.02], -0.36 [-1.46 to 0.20] and -0.67 [-1.07 to 0.42]). No differences were found at other followings time points. Viremic patients and those diagnosed late or at an older age showed a tendency towards delayed growth but no significance could be found.

Conclusion: In our study in an European cohort, prompt ART initiation improved growth status of HIV-infected children. The effect of the immunological status seems to impact growth in early stages of life. Larger studies are warranted to evaluate the role of treatment / viral suppression on long- term growth in children.

P1-375**SOAR Study: New approaches to managing social skills deficits in Turner Syndrome**

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Background: Turner Syndrome (TS) is a sex chromosome aneuploidy (45,X) associated with social skill difficulties. The 2016 Cincinnati clinical care guidelines recommend that the Program

for the Education and Enrichment of Relational Skills (PEERS) social skills intervention is piloted. PEERS has previously been used in face-to-face interventions with male adolescents with autism spectrum conditions. This pilot project will be the first to examine the feasibility and acceptability of the PEERS protocol online.

Methods: The PEERS consists of 14 weekly lessons and runs two concurrent groups; one for the young women and one for parents. The young person lessons are structured to provide didactic instruction as well as social skill rehearsal. PEERS has been modified to be delivered primarily online. Face-to-face sessions took place at the start, middle and end of the program. All other sessions were conducted online using Adobe Connect Meetings.

Participants were screened using the Strengths and Difficulties Questionnaire (SDQ) Peer scale to measure deficits in social performance (parent report) and the PEERS screening interview assessed motivation to improve social competence (young person and parent).

The pilot used an uncontrolled study design with multiple-case tracking. The primary outcome measure (Social Competence with Peers; SCP) assessed social performance at 9 time-points (3x pre-pilot, 3x during pilot, 3x post-pilot). Secondary outcome measures assessed pre-post changes in social knowledge, anxiety, self-esteem and autistic symptomatology using standardised questionnaire, and evaluated intervention acceptability.

Results: PEERS was piloted with 7 young women with TS aged 17-20 with a verbal IQ above 70. At baseline participants scored in the abnormal range on the SDQ peers scale ($t_{(6)}=4.66$, $p=0.003$) compared to female population norms and were highly motivated to improve their daughter's social functioning.

After the intervention social performance was significantly improved on the SCP by parent report ($p=0.045$; $\delta=0.64$). Gains were maintained at follow up. Significant improvements were observed in social knowledge ($p<0.0001$; $\delta=4.25$) and autistic symptomatology ($p=0.036$; $\delta=0.46$). No significant changes were found in standardised self-report measures of anxiety and self-esteem.

Adherence to the intervention was high (>86%) and 100% of participants rated PEERS as 'very helpful' and reported improvements in the young person's social ability.

Discussion: The young women and their parents were highly motivated to improve their daughter's social functioning. Online administration will substantially broaden the accessibility of social skills interventions in a cost-effective way to more young women with TS and other rare genetic disorders.

P1-376

Noonan Syndrome (NS) spectrum panels should include mutations in *LZTR1* gene

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Background: A few patients with NS have been reported to harbour pathogenic mutations in *LZTR1* gene. RAS regulation by *LZTR1*-mediated ubiquitination provides an explanation for the role of *LZTR1* in human disease. Mutations in this gene could hence lead to NS phenotype. Three patients with mutations in this gene and compatible NS phenotype are herein described.

Case 1: A 5 year-old boy with bilateral cryptorchidism, supravalvular pulmonary stenosis, low set and posteriorly rotated ears, curly hair, low posterior hairline, hypertelorism and *pectus excavatum*. No mutations were identified in genes *PTPN11* and *SOS1* through direct sequencing. Whole exome sequencing (WES) identified a heterozygous missense mutation in gene *LZTR1*: NM_006767:c.742T>C (p.Gly248Arg), (exon 8; Kelch 4 functional domain). A deleterious effect of this mutation has been predicted by bioinformatic algorithms and has been previously described to cause NS.

Case 2: A 4 year-old boy with short stature (-3.2 SD), pulmonary valve stenosis, right cryptorchidism, Von Willebrand disease, down slanted palpebral fissures, low set ears and posterior hairline and hypertelorism. Sanger sequencing of 8 genes associated to NS identified no mutations; however, WES localized a homozygous missense mutation in the gene *LZTR1*: NM_006767:c.2074T>C (p.Phe692Leu), (exon 18). This mutation has not been previously described and is predicted to have a deleterious effect on the protein.

Case 3: An 8 year-old boy with almond shaped eyes, cupped shaped and low set ears, low posterior hairline, *pterigium colli*, wide thorax, speech delay and a mother with typical NS facial features and a stature of -1.9 SD. A multigene panel for rasopathies found no mutations, but a subsequent WES, showed a heterozygous missense variant in *LZTR1*: NM_c.730T>C(p.Ser244Pro), (exon 8; Kelch 4 functional domain) that is maternally inherited. This variant has not been previously described. Nevertheless, multiple *in silico* predictors classify this variant as deleterious. Familial segregation suggests the pathogenicity of this variant.

Conclusions: Whole exome sequencing rather than direct sequencing of individual genes should be the approach for syndromic phenotypes associated to various genes. Albeit functional studies are still required to confirm causality of each mutation in

LZTR1 leading to NS, this gene ought to be incorporated into RASopathy genetic panels. Patients with pathogenic mutations in *LZTR1* seem to exhibit characteristic NS facial features but variable expression in heart, stature and neurodevelopment, where dominant inheritance may associate a milder phenotype.

P1-377**International consensus: Ovarian tissue cryopreservation in young Turner syndrome patients. Outcomes of an ethical Delphi study including 55 experts from 16 different countries**

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Summary Answer: The majority of the expert panel states that ovarian tissue cryopreservation (OTC) should be offered to young females with Turner syndrome (TS)

Background: OTC is a valid option to preserve the fertility of young females at risk of iatrogenic premature ovarian insufficiency (POI). Offering OTC to females with a genetic cause of POI seems a logical next step. One of the most common genetic disorders related to POI is TS. Due to an early depletion of the ovarian reserve, most females with TS are confronted with infertility before reaching adulthood. However, before offering OTC as an experimental fertility preservation option to young females with TS, the medical and ethical concerns need to be addressed first.

Design: A three-stage ethical Delphi study was conducted to discuss the pros and cons of OTC in young females with TS in a systematic manner. The aim of this study was to reach group consensus and to form an international standpoint based on selected key statements. The study was conducted between February and December 2018.

Methods: A mixed panel of 12 gynaecologists, 13 (paediatric) endocrinologists, 10 medical ethicists and 20 patient representatives participated in this international Delphi study. Panellists were selected because of their expertise in TS, fertility preservation or medical ethics. In the first two rounds, all experts were asked to rate and rank 38 statements and 155 supporting arguments regarding OTC in females with TS. Opinions were swayed via repetitive feedback after each round. The selection of key statements was based on strict inclusion criteria.

Results: A total number of 46 participants from 16 different countries completed the first Delphi-round (response rate 84%). Based on strict selection criteria, 6 key statements were selected and 13 statements were discarded. The remaining 19 statements and 2 additional statements submitted by participants were re-evaluated in the second round by 41 participants (response rate 76%). The analysis of the second survey resulted in the inclusion of 2 additional key statements. The final selection of key statements was approved by 96% of the participants. After the pros and cons were discussed and the main arguments were selected, the majority of our expert panel (75%) believed that OTC should be offered to young females with TS in a safe and controlled research setting.

Arguments that focused on beneficence, autonomy, and justice outweighed statements regarding non-maleficence. The remaining participants (25%) did not object, but chose to remain neutral.

P1-378**Vascular Anomalies And Aortic Dilatation in Turner Syndrome Study In A Large Cohort Of Young-Adult Patients**

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Background: Patients with Turner Syndrome (TS) are at high risk for congenital heart disease (CHD), aortic dilatation and dissection with increased mortality and morbidity. Thoracic gadolinium-enhanced MRI angiography allows clear imaging of all great vessels and revealed a spectrum of silent vascular anomalies (VA), both venous and arterial, undetected at Echocardiography.

The aim of this study is to retrospectively evaluate the prevalence of VA and aortic dilatation in TS, particularly in patients without CHD.

Methods: A cohort of 115 patients (mean age 24,4 years; range 16 - 42,6 years) with genetically confirmed TS and no evidence of CHD at Echo and MRI was analyzed. Echocardiography and MRI evaluations were collected to obtain a complete cardiological evaluation. The aortic diameters measured at MRI were indexed for the patient's Body Surface Area (BSA) and compared with reference values for aortic dilatation validated by Roman et al (1).

Results: Vascular anomalies were detected in 44 patients (38,3%). Elongation of the transverse aortic arch (ETA) was detected in 32 patients (27,8%), aortic kinking in 11 patients (9,6%), right subclavian artery in 7 patients (6,1%), pseudocoarctation in 13 patients (11,3%) and left superior vena cava in 2 patients (1,7%). Aortic dilatation was detected in 17 patients (14,8%) and was significantly associated with VA (OR=4; p = 0,026) and age (OR=1,1; p = 0,028).

The mean BSA-indexed diameters were significantly higher in subjects with VA than in subjects without. ETA was the vascular anomaly with the greatest influence on aortic dilatation (OR=4,5; p<0,015). No significant association was found between aortic dilatation and karyotype, phenotype, renal anomalies, growth hormone and estrogen replacement therapy.

Conclusions: The study shows that aortic dilation in TS can occur even without CHD and is significantly associated with silent vascular anomalies, detected by MRI. ETA was associated with a high risk of dilatation, both at the level of the ascending aorta and

of the sinuses of Valsalva. Given the high prevalence of unexpected vascular anomalies in patients with TS and their correlation with aortic dilatation, it is mandatory to recommend a thoracic MRI to better evaluate the cardiovascular risk for TS patients, particularly before any attempt at pregnancy.

1) M. J. Roman, R. B. Devereux, R. Kramer-Fox, and J. O'Loughlin, "Two-dimensional echocardiographic aortic root dimensions in normal children and adults," *Am. J. Cardiol.*, vol. 64, no. 8, pp. 507–512, 1989.

P1-379

Adult height prediction by bone age determination in children with idiopathic growth hormone deficiency (IGHD): Analysis of KIGS data

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Background: The precision of adult height prediction by bone age determination in children with idiopathic growth hormone deficiency (IGHD) is unknown.

Patients and Methods: The near adult height (NAH) of patients with IGHD with prepubertal onset of growth hormone treatment (GH) in the KIGS database was compared to adult height prediction based on bone ages (BA) >7 years using the Bailey Pinneau (BP) or Tanner-Whitehouse 2 (TW2) method. The study population included 315 children (baseline: 122 girls and 193 males with mean age 10.4y and 11.3y, respectively) with height prediction based on BP method and 121 children (baseline: 22 girls and 99 boys with mean age 10.6y and 10.8y, respectively) with height prediction based on TW2 method. Multiple linear regression analyses adjusted for age at GH start, mean dose of GH treatment, years of GH treatment, and maximum GH peak in GH stimulation test were calculated.

Results: The difference between NAH and target height (median) was -3.3 cm in girls and -3.0 cm in boys. Adult height prediction did not differ significantly ($p=0.36$) between BP and TW2. The adult height prediction correlated between BP and TW2 at baseline ($r=0.74$, $p<0.001$), at 1 year of GH treatment ($r=0.82$, $p<0.001$) and at the last performed BA ($r=0.87$, $p<0.001$) on average 6 years after baseline. The mean underestimation of NAH based on the BA method was at baseline 4.0 ± 0.5 cm in girls and 4.4 ± 0.4 cm in boys, at 1 year of GH treatment 2.0 ± 0.3 cm in girls and 0.5 ± 0.3 cm in boys, while at last BA NAH was overestimated in mean by 0.4 ± 0.4 cm in girls and 3.7 ± 0.3 cm in boys. The mean underestimation of NAH based on the TW2 method was at baseline 1.4 ± 1.3 cm in girls and 6.6 ± 0.6 cm in boys, at 1 year of GH treatment NAH was overestimated in girls 0.9 ± 0.6 cm in girls and underestimated 3.8 ± 0.4 cm in boys, while at last BA determination NAH was overestimated in mean by 1.1 ± 0.9 cm in girls and 4.5 ± 0.5 cm in boys.

Conclusions: Height prediction by BA determinations at onset and in the first year of GH treatment underestimates NAH in prepubertal children with IGHD at onset of treatment. In contrast, height prediction by BA at pubertal age in IGHD children treated with GH for a mean of 6 years overestimated NAH.

P1-380

A new model of adult height prediction validated in boys with constitutional delay of growth and puberty

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Background: For children with retarded bone ages such as in constitutional delay of growth and puberty (CDGP) there are no specific methods to predict adult height based on bone age. Widely used methods such as Bayley-Pinneau (BP) tend to overestimate adult height in CDGP. Therefore, we aimed to develop a specific adult height prediction model for boys in pubertal age with retarded bone age >1 year.

Methods: Based on the adult heights of 68 males (median age 22.5 years) a new height prediction model was calculated based on 105 height measurements and bone age determinations at a median age of 14.0 years. The new model was adapted for the degree of bone age retardation and validated in an independent cohort of 32 boys with CDGP. The new model for predicting adult height was based on the following procedure: Achieved adult height was divided by the measured height at the recent bone age determination. For every bone age, the median of these calculated factors at the respective bone age was chosen. Afterwards, regression models (linear, exponential, potential, logarithmic and hyperbolic) were calculated based on the median factor to predict adult height of each bone age. The model with the highest r^2 was chosen.

Results: The BP method led to an overestimation of adult height (median +1.2cm; $p=0.282$), which was more pronounced in boys with a bone age retardation ≥ 2 years (median +1.6cm; $p=0.027$). In the validation study, there was no significant difference between reached and predicted adult height based on the new model ($p=0.196$), while the BP model led to a significant overestimation of predicted adult height (median +4.1cm; $p=0.009$).

Conclusions: The new model to predict adult height in boys with CDGP provides novel indices for height predictions in bone ages >13 years and is adapted to different degrees of bone age retardation. The new prediction model has a good predictive capability and overcomes some of the shortcomings of the BP model.

Table 1: Coefficients to predict adult height in boys with retarded bone age >1 year

Bone age [years]	BP	New model for bone age retardation >1 and <2 years	New model for bone age retardation ≥ 2 years
11.0	82.3%	82.5%	82.6%
11.5	83.2%	83.7%	84.1%
12.0	84.5%	85.4%	85.8%
12.5	86.0%	87.2%	87.5%
13.0	88.0%	89.1%	89.3%
13.5	-	91.1%	91.2%
14.0	-	92.8%	93.1%
14.5	-	95.2%	95.2%
15.0	-	97.5%	97.3%
15.5	-	99.9%	99.6%

P1-381

The relation between Changes in Body Mass Index (BMI) and linear growth in prepubertal children: Daily Weight Gain and BMI changes in Relation to Linear Growth During Nutritional Rehabilitation of Underweight Children

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We analyzed the effect of having different BMI and BMI SDS, if any, on linear growth (HtSDS) in a cohort of prepubertal children ($n = 102$) in different BMI categories. In addition, we studied the effect of weight changes on linear growth in a randomly selected group of underweight children after nutritional rehabilitation (NR).

Subjects and Methods: All prepubertal children between 1 and 9 years presented to the general pediatric clinic because of abnormal weight gain (decreased or increased) which is not related to any acute or chronic illness were included in this cross-sectional study. Physical exam and routine lab tests (CBC, renal and liver functions, ESR, thyroid function) did not show any abnormality. Anthropometric measurements included weight, height, HtSDS, BMI, and BMI SDS. Children BMI SDS were categorized into 4 groups: Group 1: BMISDS < -2, group 2: BMISDS <-1 but >-2, group 3 BMISDS > -1 but < 2, group 4 BMISDS > 2. We evaluated the effect of weight changes on linear growth in a randomly selected group of underweight children who received NR ($n = 51$) for a year.

Results: HTSDS in children of groups 1 and 2 (underweight and at risk of underweight children) was significantly lower than HTSDS of groups 3 and 4 (normal and overweight children). HTSDS in children of group 4 was significantly higher than the HTSDS of children in group 3.

After NR 60% of underweight children increased their BMISDS and 43% increased their HtSDS. Children who had weight gain >7g/d over the whole period of follow-up (average normal weight gain for the average age and gender is 6.5g/d) ($n = 14$) increased

their BMISDS and HtSDS significantly after versus before NR, whereas, BMISDS and HtSDS did not increase significantly in the group of children who had weight gain < 7 g/day. 28 children out of 51 improved their BMISDS after nutritional rehabilitation (group A) and 23 did not (Group B). Group A had higher weight gain per day (8.6 ± 5.8 g/day) versus group B (3.3 ± 2.2 g/d). Height growth velocity was significantly higher in Group B (7.4 ± 3.6 cm/yr) vs A (5.7 ± 2.8 cm/yr). A significant correlation between BMISDS and HtSDS ($r = 0.72$, $p < 0.001$).

Conclusion: It appears that calculating the weight gain per day, BMISDS and HtSDS are clinically useful to detect the effect of weight gain on linear growth and monitor nutritional management.

P1-382

Nutritional Requirements in Prader Willi Syndrome Children Treated with Growth Hormone Under Two Years of Age

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Background: Prader Willi Syndrome (PWS) patients under treatment with growth hormone (GH) have a better body composition and cognitive performance than untreated patients. The 2013 guideline recommended to start this treatment as soon as possible, for that reason 14 toddlers have been included in our center. Classically a 25% decrease in the caloric intake of PWS patients has been recommended to avoid obesity. However, from clinical practice observation, we hypothesized that the caloric needs in these patients could be higher the first 2 years of age.

Objectives: To know the variation of BMI in patients with PWS under 2 years of age treated with GH and to determine their caloric intake.

Methods: Retrospective observational study comparing PWS patients under 2 years of age treated with GH in our hospital (G1) with a control group of a historical cohort of PWS patients with who did not receive treatment with GH before the age of 2 (G2). The caloric intake of G1 was obtained by a 24h intake questionnaire.

Results: The analyzed data correspond to 12 patients in G1 (58.3% males, 66.7% paternal deletion and 33.3% uniparental disomy) and 6 patients in G2 (50% males, 50% paternal deletion, 33.3% uniparental disomy and 16.7% genomic imprinting). The median age of onset of GH was 10.75 months (IQR 9-16) in G1 and 28.2 (IQR 27-34) in G2. The caloric intake of G1 patients was 663+/-122.35, 701.8+/-80.97, 711.8+/-105.76, 791.8+/-92 and 910.4+/-128.92 kcal per day on average at 9, 12, 15, 18 and 24 months respectively. Weight, height and BMI were compared in both groups at 9, 12, 15, 18 and 24 months. G1 patients show higher height in all the determinations. BMI tendency in G2 was to increase, whereas in G1 was to decrease progressively ($p<0.05$).

Conclusions: GH treatment in PWS patients under 2 years of age affects their BMI. It is important to adjust the caloric intake of these patients in order to adequate to their current needs. It is required to verify this results in longitudinal studies.

P1-383

Cardiovascular Anomalies and Association with Karyotypes in Turner syndrome in Taiwan: one medical center experience

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Background: Turner syndrome (TS) is caused by complete or partial of the second sex chromosome and characterized by growth failure, primary ovarian failure, the constellation of the lymphedema sequence, characteristic facial features, left-sided cardiac anomalies, renal anomaly, and skeletal anomalies. Among all of the associated traits, cardiovascular abnormalities are common in TS and an important cause of early mortality. Hence, our aim is to investigate the correlations between the cardiovascular phenotype and karyotype in TS in Taiwan.

Patients and Methods: We conducted a retrospective analysis of 105 Turner syndrome patients, aged 6-43 years old, from January 1994 to December 2018 at the Division of Pediatric Endocrinology & Genetics, Chang-Gung Memorial Hospital in Taiwan. The patients were categorized into 2 groups according to karyotype, each were comprised with X chromosome monosomy(45, X) and the other X chromosome abnormalities(including mosaicism and structural aberrations).

Most of the patients were evaluated with echocardiography (n=88, 83.8%), coronary computed tomography angiography (CTA), and/or cardiovascular magnetic resonance imaging (CMR)(n=58, 55.2%).

Results: Cardiovascular malformations were found in 29 (27.6%) TS patients. Aortic dilatation (AD) was the most common cardiovascular malformation 18.2% (16/88), composed of 37.5% (6/16) aortic root dilatation only, 25% (4/16) ascending aortic dilatation only, and 37.5% (6/16) both aortic root and ascending aortic

dilatation. The overall prevalence of bicuspid aortic valve (BAV) was 6.8% (6/88) and the monosomy X group had higher prevalence in aortic dilatation($p=0.002$) and BAV($p=0.007$). Mitral valve regurgitation(MR)(6.8%), tricuspid valve regurgitation(TR) (6.8%), coarctation of aorta(CoA)(3.4%), aortic regurgitation(AR) (3.4%), aortic stenosis(AS)(2.3%), mitral valve prolapse(MVP) (2.3%), atrial and ventricular septal defect(ASD and VSD)(both 1.1%), right-sided aortic arch(1.1%), and partial anomalous pulmonary venous return(PAPVR)(1.1%) were noted with decreasing frequency, and there were no significantly difference between the study groups among the prevalence of the above cardiovascular malformations.

Conclusion: The incidence of bicuspid aortic valve and aortic dilatation is higher in women with 45, X karyotypes. Patients with X monosomy should have surveillance for aortic root dilatation, treatment for hypertension and prophylactic medical therapy with timely surgical consultation to reduce the incidence of aortic dissection.

P1-384

Pubertal induction amongst girls with Turner Syndrome: a review of changing practice over 10 years

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Background: Pubertal induction with incremental doses of oestrogen replacement is an important component of care offered to hypogonadal patients with Turner Syndrome (TS). Low dose oral ethinylestradiol (EE) has been extensively used in the UK but natural 17-β oestradiol (more physiological, cheaper and easily monitored in blood) is becoming increasingly popular.

We undertook this audit to compare the efficacy and acceptability of oral (EE) and patch (Evorel) oestrogen preparations used in our centre.

Subjects & Method: A retrospective audit was undertaken analysing the clinical records of all girls with TS who started pubertal induction 2008-2017, excluding those yet to start progestogens (n=27). Data is mean+/-SD.

Result: Pubertal induction was started at 13.1 ± 1.8 years and progestogen introduced at 16.1 ± 1.9 years; duration of unopposed oestrogen action was 2.8 ± 0.8 years. Eleven (40.7%) patients used oral EE, 10 (37.0%) patches and 6 (22.2%) changed from one form to the other. Where recorded, 15(62.5%) were in Tanner stage 1, 7(29.2%) in stage 2, while 2 (8.3%) were in stage 3 before induction. At introduction of progestogen, 19(82.6%) were in stage 3 and the rest in stage 4.

Height SDS (UK-WHO reference) was -2.3 ± 1.0 at pubertal induction and -1.9 ± 1.0 at completion. Height SDS change during induction was 0.5 ± 1.0 . There was no significant difference between oestrogen regimens in height SDS change (oral: 0.4 ± 1.0 , patches: 0.8 ± 1.1 , $p=0.4$).

Nine (33.3%) had pelvic USS before pubertal induction, of which there was a normal prepubertal uterus in 8 and normal

ovaries in 1. Six (21.4%) had a pelvic USS at the end of puberty; 5 had normal sized post-pubertal uterus and 1 remained infantile.

Raised ALT ($\geq 35\text{iu/l}$) with no clinical symptoms of liver disease was seen both pre- and post- puberty (2/26 and 5/25 respectively). The 2 girls with pre-pubertal raised ALT remained so after puberty. Of the 3 additional girls with deranged LFT, 2(66.7%) used EE and 1(33.3%) used patch, ($p=1.000$).

Seventeen (63.0%) patients had DEXA at transition, 2 had low bone mineral density (BMD). Both presented at 13 and 16 years with short stature and delayed puberty; both used patches. BMD status was not significantly different between oestrogen regimens ($p=0.5$).

Conclusion: Induction of puberty with oral or patch oestrogen appears to be equally effective in girls with TS. One third of girls who started on patches switched to an oral preparation. Uterine imaging was not consistently undertaken.

P1-385

Saliva might be a good alternative DNA source for whole exome sequencing to identify genetic causes of short stature

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Background: Genetics plays a strong role in height. However, for most patients, no cause for the short stature can be identified. Whole-exome sequencing (WES) is becoming an increasingly important tool for detecting novel genetic causes of short stature. Blood is the preferred DNA source for germline studies using WES. However, DNA from saliva is a more convenient and cost-effective alternative.

Objectives: We aim to identify known and novel genetic causes of short stature.

Methods: We recruited 12 children with short stature of unknown etiology. We conducted WES of the patients and their family members. Saliva samples were collected from 12 subjects with syndromic short stature. A series of DNA isolation optimization experiments were performed on the saliva samples. WES was performed on samples from optimized saliva DNA isolation and subsequent Sanger sequencing was conducted on isolated DNA from blood for the validation in trio. The average coverage for WES was 100X. We used an analysis pipeline to identify rare non-synonymous genetic variants that cause the short stature.

Results: We identified a genetic cause of short stature in 11 of the 12 patients. This included cases of CDK13-related disorder, Braraitserwinter syndrome 1, Rubinstein-Taybi 2, COHEN syndrome, Pierpont syndrome, Trichorhinophalangeal syndrome, SRMMD (Short Stature, Rhizomelic, with Microcephaly, Micrognathia, and Developmental delay), VERHEIJ syndrome, and Arthrogryposis, distal type2B (Sheldon-Hall syndrome), as well as two cases of the ZTTK syndrome.

Conclusions: This analysis represents, to our knowledge, the first comprehensive examination of WES data generated from saliva in Korea. Saliva might be a good alternative DNA source for WES to identify genetic causes of short stature. This indicates that high quality sequencing data can be derived from saliva samples for germline genetic analyses.

P1-386

Prevalence of copy number variations (CNVs) in a cohort of SGA children with persistent short stature associated with additional clinical features

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Background: Multiple factors may affect intrauterine growth leading to birth of children small for gestational age (SGA). The impact of subtle genetic alterations on both pre and post-natal growth is still largely unknown.

Objective and Hypotheses: The aim of this study was to investigate the prevalence of CNVs in a cohort of SGA children with persistent short stature.

Subjects and Methods: 26 SGA children (9.5 ± 1.2 yrs, 10F/16M) with short stature associated with dysmorphic features and/or developmental delay underwent array-CGH (aCGH) analysis.

Results: aCGH analysis showed CNVs in 50% (n=13) of short SGA children. Specifically, six patients had a microdeletion involving the following regions: 22q11.2, 8p21.2-8p12, 3q24q25.1, 19q13.11, 20q11.21q12, 15q26. In three females the same microdeletion involving 17p13.3 was found. In two patients the detected anomaly consisted of microduplication involving 10q21.3 and Xp11.3 region. In a female patient a compound microduplication was found (11q12.2 inherited from mother and Xq27.1 from father). In a boy the presence of both a microdeletion of 12p13.33 and a microduplication of 19q13.43 was observed.

Conclusions: These results show that CNVs can be detected by aCGH analysis in a large proportion of SGA children with short stature associated with additional clinical features. Interestingly, the involvement of 17p13.3 region occurs with a relative high frequency, suggesting that genes located in this region play a key role in pre and post-natal growth.

Omnitrope® (recombinant human growth hormone) in short children born small for gestational age (SGA): a long-term, phase IV study

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Background: Short children born SGA are predisposed to metabolic abnormalities. While the benefit of recombinant human growth hormone in improving height is widely recognised, it can affect carbohydrate metabolism and lead to impaired glucose tolerance during treatment. This ongoing, prospective study is assessing the long-term safety and efficacy of Omnitrope® (somatropin) in children born SGA. Here we present data from an interim analysis conducted in April 2017.

Methods: Prepubertal children born SGA were recruited according to standard criteria; those included are treated with Omnitrope® and followed at predetermined time intervals until final height is reached. Non-responders to treatment (height velocity standard deviation score [HVSDS] < +1) were withdrawn from the study after one year.

Results: Overall, 278 children were enrolled in the study; 13 discontinued after one year due to non-response to treatment; 249 completed their 2-year assessment; and 132 remained in the study at the interim analysis timepoint (median treatment duration 72.7 months). Mean (SD) age at baseline and latest visit was 7.86 (2.74) and 13.08 (3.36) years, respectively. To date, there have been no confirmed cases of new-onset diabetes mellitus. Oral glucose tolerance (2h), HbA1c, and fasting glucose levels have remained stable from baseline to latest visit; however, mean (SD) fasting insulin levels increased from 35.65 (34.69) pmol/L at baseline to 53.68 (35.93) pmol/L after 1 year and to 70.46 (45.60) pmol/L at latest visit. Auxological measurements demonstrated improvements in height parameters from baseline to latest visit, including mean height SDS (-3.39 at baseline, -2.57 at Year 1, -2.15 at year 2 and -1.74 at latest visit) and peak-centred HVSDS (-2.11 at baseline, +4.16 at Year 1, +2.23 at Year 2, and +0.19 at latest visit). Similarly, mean (SD) IGF-I SDS increased from -1.08 (1.02) at baseline to +0.64 (1.21) after 1 year and +0.53 (1.27) at latest visit. In total, 2075 adverse events (AEs) have been reported in 242 patients. The vast majority of these AEs were of mild-to-moderate intensity (99%) and not suspected to be related to study drug (96%). Serious AEs (n=125) have been reported in 68 patients; 4 (in 3 patients) were suspected as possibly related to study treatment, and one (osteonecrosis) resulted in study drug being permanently discontinued.

Conclusions: This long-term study confirms the effectiveness of Omnitrope® treatment for improving height in short children born SGA. In addition, there have been no concerning or clinically relevant safety findings to date.

Is there a QTc interval prolongation in girls and women with Turner syndrome?

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Introduction: Turner syndrome (TS) is a genetic condition which is reported to be associated with electrocardiogram (ECG) abnormalities, of which the rate-corrected QT interval (QTc) is the most common indicated deviation. Our objectives were to gain more insight in the prevalence of QTc-prolongation using both Bazett's and Hodge's correction formulas in patients with TS of all ages and to investigate whether QTc prolongation is more prevalent in patients with a monosomy 45,X compared to patients with other karyotypes.

Methods: Girls and women with TS visiting the outpatient clinics of our tertiary medical centre were included in this study. Data on age, length, weight, karyotype, systolic and diastolic blood pressure, hypertension, cardiac malformations and comorbidities were obtained from the medical records. Karyotype (determined in blood and buccal mucosa (only in 45,X)) was divided into two groups: monosomy 45,X and other karyotypes. QT intervals of computerized and printed 12-leaded ECGs were measured manually by two researchers. A QTc interval of >450 ms for girls and >460 ms for women was considered prolonged. Prevalence of QTc prolongation was compared to the general population.

Results: In total 125 girls (age 1-18 years) and 225 women (age 19-65 years) were included. Monosomy 45,X was present in 33% of the patients. The mean QTc interval using Bazett's formula was longer compared to Hodge's formula (420 ± 25 ms versus 400 ± 20 ms, $p<0.001$). In total, 5% of the population had a prolonged QTc interval using the Bazett's formula (4% in girls and 6% in women) and 0% using Hodge's formula (1% in girls and 0% in women), which is in line with the prevalence reported in the normal population. Girls with TS had a higher basic heart rate, regardless of cardiac comorbidity, and a lower QTc interval compared to women with TS, regardless of the correction formula. Furthermore, patients with a monosomy 45,X karyotype had a higher basic heart rate compared to the patients with other karyotypes. Yet, the QTc interval was not significantly longer in patients with monosomy 45,X compared to patients with other karyotypes, when using both formulas.

Conclusion: This study shows that the QTc interval in patients with TS is not prolonged compared to the normal population using both Bazett's and Hodge's formulas, in contrast to what other studies have stated in small cohorts. Patients with monosomy 45,X show no clinically relevant QTc prolongation compared to other karyotypes.

P1-389

Eight years of growth hormone treatment in a patient with Schaaf-Yang Syndrome

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Background/Aims: Schaaf-Yang syndrome (SYS) is a rare disorder caused by a truncating mutation in the gene MAGEL2, located in the Prader-Willi critical region on chromosome 15. SYS is characterized as a Prader-Willi-like (PWL) disorder, with neonatal hypotonia, feeding problems in early infancy and intellectual disability, obesity and behavioral problems throughout childhood. In this case report we describe a 15-year-old girl, receiving GH treatment since age 6 because of partial GH deficiency. She was diagnosed with SYS at 12 years of age.

Methods: Medical records were retrospectively reviewed. Data on height, weight and BMI were available for the entire eight years of GH treatment. Data on body composition were only available for the most recent four years since she was diagnosed with SYS.

Results: The patient was extensively evaluated by the Dept. of Clinical Genetics and Pediatric Neurology, because of psychomotor delay. Whole exome sequencing (WES) eventually showed a frameshift, de novo mutation in the MAGEL2 gene. After 8 years of GH treatment, height SDS had increased from -3.95 to -1.11. BMI improved from +1.53 SDS to -0.09 SDS. After being diagnosed with SYS, she received multidisciplinary care by the Dutch PWS team. In these 4 years, fat mass percentage (fat%) improved from 44% to 31.2%, a decrease of 1.21 SDS and lean body mass (LBM) increased from -2.96 SDS to -2.06 SDS.

Conclusion: This patient with SYS shows a normalization of height SDS, a significant decrease in fat% SDS and increase of LBM SDS during 8 years of GH treatment. Further studies need to confirm the effectiveness of GH treatment in patients with SYS.

P1-390

Genetic Evaluation of Idiopathic Short Stature

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Introduction: Short stature is a multifactorial condition caused by both genetic and environmental factors. Genetic causes include chromosomal disorders and diseases inherited by monogenic and multifactorial inheritance. The purpose of genetic evaluation in short stature is not only for diagnosis, but also to provide additional information to the patients and their families about prognosis of the disease, treatment approaches and genetic counseling.

Aim: This study aims to investigate genetic etiology by using cytogenetic, molecular cytogenetic and next generation sequencing methods in patients with idiopathic short stature.

Patients and Method: In this study, 189 patients, in whom chronic diseases, hormonal disorders and skeletal dysplasia were excluded, and diagnosed as idiopathic short stature were included in the study. We did an algorithmic approach for genetic screening. In the first phase cytogenetic investigations were done and chromosomal anomalies were excluded. Then SHOX gene deletions were investigated by fluorescent *in situ* hybridization and possible submicroscopic deletions and duplications by a-CGH technique. After these evaluations 41 patients, found to have normal chromosomal segments, underwent to next generation sequencing of the Ion Torrent platform with 25 gene-containing panel-gene tests. Gene panel consisted of 10 genes associated with short stature (*GH1, GHR, GHRH, GHSR, IGF1, IGF1R, IGFA, IGFBP3, SHOX, STAT5B*) and 15 genes (*POU1F1, PROP1, HESX1, LHX3, LH4, IGSF1, OTX2, BMP4, SHH, WDR11, FGFR1, FGF8, PROKR2, SOX3, HHIP*) associated with isolated or multiple pituitary hormone deficiency (MPHD).

Results: Of the 189 patients with short stature, 16(8.5%) had chromosomal anomaly, 1 had microdeletion in the *SHOX* gene with FISH examination, and 1 patient had a deletion of 2.7MB in the 5q32 region with a-CGH assay. In five patients, 5 different variations were detected (*BMP4, GHR, IGSF1, LHX4 and PROKR2*) (one in short stature genes, 4 in MPHD genes). One of these mutations was novel, one of them was previously defined and 3 of them were found in databases. The changes that were thought to be of clinical importance were confirmed by Sanger sequencing method. It was shown that 4 heterozygous changes found in the segregation analysis were also found in the healthy individuals in the family and in one patient with homozygous change, the parents were shown to be heterozygous carriers.

Conclusion: Short stature for gene panel test was first evaluated in Turkey. We recommend cytogenetic examination before molecular analysis to exclude chromosomal anomalies and microdeletions. Because short stature has a wide genetic spectrum, we think that the targeted panels are not sufficient. We propose whole exome or whole genome sequencing analysis with a healthy control group and the index patients and parents.

P1-391

Foramen magnum stenosis (FMS): neuroradiological aspects before and after cervical decompression in paediatric patients with achondroplasia (ACH). The 'Achondroplasia Multidisciplinary Gaslini's Group' (AMGG) Istituto Giannina Gaslini, Genova, Italy: Child Neuropsychiatry Unit, Neuroradiology Unit, Department of Paediatrics, Neurosurgery Unit, Orthopedic Unit, Rehabilitation Unit, Pulmonary Disease and Allergy Unit

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The identification of anamnestic, clinical and instrumental data indicative of pathological FMS plays a pivotal role in the prevention of ACH complications.

Objective: identify key crano-cervical junction(CCJ)neuroradiological features for the surgical choice and for the neuroradiological decompression outcome.

Methods: from a total of 191 patients, we selected 24 subjects with ACH (age:<4years), who performed a first brain MRI and/or CT. Patients were divided into 2 groups: surgically treated patients (STP=15/24) and non-surgically treated patients(NSTP=9/24). The data were compared with a control group(CG) of 24 children of the same age and with a group of ACH patients surgically treated at an age of more than 4 years (ACHPST>4AA, 5/191). Antero-posterior cervical osteo-ligamentous diameter (APCOL-D), anteroposterior cervical bone diameter (APCB-D), degree of cervical stenosis (grade 0, 1, 2, 3, defined respectively on the basis of the increase in stenosis and grade 4A and 4 B defined according to the degree of stenosis in association with myelopathy), posterior margin of the prominent foramen magnum (prominence PMPFM), posterior arc of prominent C1, hypertrophy of soft tissues, occipital bone spur, orientation of the posterior edge of the foramen magnum, OS odontoideum, were evaluated by brain MRI.

Results: 33.3% of subjects who performed the first MRI in the first 6 months of life have myelopathy (stenosis 4A and 4B). All STP have cervical stenosis of grade>2, while the NSTP have degrees< 2. Grade 1 is equally represented in STP and NSTP. The APCOL-D is significantly lower in the STP vs CG ($P \leq 0.0001$) and in the STPvsCG ($P \leq 0.001$), while there is no significant difference between STPvs NSTP. APCOL-D is significantly lower in the STPvsNSTP, STPvsCG ($P=0.0001$) and NSTP vs CG ($P=0.001$), with an OR=3.95 ($P=0.02$). Prominence PMPFM is significantly associated with surgery ($p=0.003$), while no other qualitative parameters are significantly associated. In STP there is a significant increase of APCOL-D and APCB-D ($p = 0.0001$).

Conclusions: brain MRI is crucial in the preventive diagnosis of complications (screening role). The importance of performing MRI in the first 6 months of life has been highlighted. The most important radiological parameters for surgical choice are: prominence PMPFM, the APCOL-D (values<7.6mm determine a risk of

surgical therapy 4 times higher) and the degrees of stenosis>2. STP have a very good radiologic decompression outcome. The data of this pilot study will be correlated with multidisciplinary approach, useful in particular in the evaluation of grade1 stenosis (still grey area).

P1-392

Do children and adolescents with idiopathic short stature show postural alterations? Possible influence of SHOX haploinsufficiency in a pilot study

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Purpose: Needs in terms of quality of life (QoL), consisting of physical, emotional and social domains, represent a hot spot in idiopathic short stature (ISS). Between ISS, it is estimated that 12% can have SHOX deficiency. Furthermore, SHOX deficiency can affect posture and GH treatment ameliorate their QoL. Although scientific research has investigated many fields of the physical domain, very few studies highlighted how this pathological condition may affect posture. The aim of this study was to evaluate postural characteristics in patients with ISS.

Methods: 16 children and adolescents with ISS (8 males; 8 females, age mean: $11,06 \pm 3,02$ years; height: $129,31 \pm 15,19$ cm; weight: $28,81 \pm 7,93$ kg) were recruited at the University Pediatric Unit of Palermo. Each participant performed a posturographic assessment using the freeMed® baropodometric platform (Sensor Medica®) which included a baropodometric test and a stabilometric test in order to evaluate plantar features and body balance, respectively. Data were analyzed using Statistica Software 12 (StatSoft®).

Results: For the baropodometric test, the sample showed a non-physiological plantar pressure distribution with a prevalence of pressure on left foot compared to right foot (56% vs. 44% respectively). Moreover, our results indicated that the sample reported an alteration on the pressure distribution between forefoot and rearfoot (45% vs. 55% respectively) for both feet. As concern the stabilometric test, our results showed a greater significant energy expenditure in order to control body balance (i.e. Sway Length / Sway Area ratio >1). Two of these ISS patients were later identified as SHOX deficiency.

Conclusions: The findings of the present pilot study confirmed our research hypothesis and results suggest that in children with ISS the pathological physical characteristic could influence the postural profile. Considering these preliminary outcomes, we deem necessary to conduct further investigations concerning the relationships between ISS and body posture and to study the real impact of SHOX haploinsufficiency on postural profile of ISS patients.

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P1-393

Evaluation of body composition and resting metabolic rate in children with growth hormone deficiency

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Background/Aims: It is known that growth hormone regulated metabolic processes, including lipid metabolism and the amount of adipose tissue. The purpose was to study metabolic rates at rest in children with growth hormone deficiency (GHD) and their relationship with lipid and hormone levels.

Objective: To analyse the body composition and resting metabolic rate (RMR) among prepubertal children with GHD

Patients and Methods: The 20 children with GHD (11 boys, 9 girls, Tanner stage 1; aged 5-10 yr, median 6,75 years) were observed before growth hormone treatment. We investigated the lipid profile, IGF-1 level, evaluated the body composition using the Tanita (Japan) body composition analyzer BC-418MA and determined the RMR using the indirect calorimetry method in all children. We used the RMR indicator adjusted for the lean mass (LM) - RMR/LM and coefficient of variation (CV)

Results: Among 20 patients with GHD all showed increased metabolism. We observed high resting metabolic rate: RMR 1016 kkal [961; 1025], RMR/LM 68.1 kcal/kg [56; 75], increase coefficient of variation (CV) 23.8% [8.5, 32.4]. Body fat percentage was 19% [15.6; 19.8]. Correlation analysis revealed average positive correlation between the amount of SDS BMI and RMR/LM ($r = 0.54$, $p < 0.05$). The correlation analysis of the RMR/LM did not reveal its connection with blood lipid and IGF-1 levels.

Conclusions: Prepubertal patients with growth hormone deficiency in our study revealed increased resting metabolic rate, may be associated with low lean mass. No correlation between the metabolic rate, lipid level and IGF-1 were observed.

Pituitary, Neuroendocrinology and Puberty

P1-394

Next Generation Sequencing in GnRH deficient patients with congenital hypogonadotropic hypogonadism: Novel findings in *KAL1*, *SRA1*, *WDR11*, *FGFR1*, *CHD7* and *PROP1* genes

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Objective: Congenital hypogonadotropic hypogonadism (CHH) is a rare genetic disease caused by GnRH deficiency and characterized by absent or incomplete puberty with infertility. The identification of the genetic cause in this group of patients through the use of next generation sequencing (NGS) can assist to the clinical management.

Methods: Seven GnRH deficient nonrelated Cypriot probands were studied (six male and one female) so as to determine the frequency and distribution of GnRH deficiency mutations and their detailed reproductive phenotypes. All patients underwent whole exome sequencing (WES) by NGS and the returned data was filtered for genes with biological involvement in the GnRH neuronal system and CHH. The candidate mutations were confirmed by Sanger sequencing and *in silico* computational algorithms and structural analysis was performed for the predicted pathogenicity of the alterations at the protein level.

Results: Molecular analysis of the six male and one female GnRH deficient nonrelated Cypriot patients revealed novel mutations in previously reported genes with biological implication in the development of the disorder. Mutations in four nonrelated male patients included the novel X-linked recessive p.Qln82stop in *KAL1*, the novel *WDR11* autosomal dominant p.Leu244Pro in an anosmic CHH/Kallmann Syndrome patient and the novel autosomal dominant p.Pro186Ala and p.Arg822Cys in the *FGFR1* gene. An 18 yr old male was also identified to share the novel *CHD7* autosomal dominant p.Arg2400Trp in compound heterozygosity with the novel *PROP1* recessive p.Arg112Gln. Lastly, the novel p.Ile179Thr in the *SRA1* gene was identified in a 19 yr male and a 30 yr female in the heterozygous and homozygous state, respectively.

Conclusion: This report embraces the description of novel mutations in a series of genes known to be implicated in the biological development of CHH. The identification of such genetic malformations can be very informative for the management and future planning of these patients.

P1-395

Presentation and diagnosis of childhood onset combined pituitary hormone deficiency: A single center experience from over 30 years

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Background: We describe the incidence, etiologies and clinical features of combined pituitary hormone deficiency (CPHD) in pediatric patients from a single tertiary center.

Methods: The cohort comprised of patients with CPHD, treated in the Helsinki University Hospital between 1985 and 2018. They were identified through an ICD-9/ICD-10 code search, and the clinical data were recorded from the patient charts.

Results: Among the 120 patients (3.56 patients/year) with CPHD, the most common etiology was intracranial tumors and their treatment (n=64, 53%; mean (SD) age at presentation for endocrine investigations, 9.3 ± 4.3 yrs (n=60)). Forty-five patients (38%) had an intrinsic disease (isolated hypopituitarism or syndromic) and their mean age at presentation for endocrine investigations was of 3.9 ± 4.2 years (n=41). Half of them (23/45) had presented with neonatal signs of hypopituitarism, including hypoglycaemia, jaundice or micropenis/cryptorchidism and 32 (71%) exhibited extrapituitary phenotypes. Nearly all of the patients (38/39) with MRI investigated had an abnormal brain MRI. There were four families with more than one member with intrinsic hypopituitarism, three of which had a molecular genetic diagnosis. One patient with genetically defined hypopituitarism had died at the age of three years despite adequate hormonal treatment.

Conclusions: We conclude that (i) the diagnoses of intrinsic hypopituitarism predominate in younger patients with CPHD; (ii) early signs of pituitary hormone deficiency were present in a significant proportion of patients with intrinsic CPHD, and thus, should be recognized by all pediatricians, since (iii) congenital CPHD continues to be associated with significant mortality. Genetic investigations of familial cases are currently underway.

P1-396

The Relationship Between Precocious Puberty and Premature Thelarche with Serum Irisin Levels

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Background and Aims: Irisin is a newly discovered adiponectin that occurs by the cleavage from a transmembrane protein called "Fibronectintype III domain containing 5" (FNDC5). Previously, there was a change in irisin levels in different prepubertal and pubertal stages. Although the mechanisms that trigger the onset of puberty cannot be explained yet, there is a hypothesis that peripheral adipose tissue and adipokines secreted there may induce the initiation of puberty by stimulating the central neural network. The aim of our study was to compare the levels of irisin in prepubertal and pubertal children and to determine whether adiponectin could be used as a marker.

Methods: The study was performed in 94 girls, with 33 precocious puberty, 31 premature thelarche and 30 prepubertal volunteers. Age and body mass index (BMI) standard deviation score (SDS) groups were generated. The levels of irisin were compared between groups. Also examined the correlations between irisin and age, BMI-SDS, height-SDS, weight-SDS, bone age, uterine axis, right ovary size, left ovary size, basal FSH, basal LH, peak FSH, peak LH and estradiol (E2). With multiple regression analysis the most important factors that influence the level of the irisin have been identified.

Results: The table comparing the precocious puberty, premature thelarche and control group is as follows (Table 1). There was a positive correlation between irisin and BMI-SDS, height-SDS, weight-SDS, bone age, uterine axis, right ovary size, left ovary size, basal FSH, basal LH, peak FSH and peak LH. In the multiple regression analysis, it was observed that the most important factor associated with irisin was the peak LH level, respectively, and age and BMI-SDS respectively.

Conclusions: The irisin levels were significantly higher in the precocious puberty group than the premature thelarche and the control group. Although there is a finding supporting the hypothesis that the elevation of irisin may be effective on the onset of puberty, it is not possible to confirm this hypothesis with this study. It can also be thought that increased muscle and fat tissue during puberty may play a role in increasing irisin levels. In spite of this, it was concluded that this increase in irisin levels could be useful in the diagnosis of precocious puberty and could be used as a marker after higher number of patients studies.

P1-397**Questioning the Value of Brain MRIs in the Evaluation of Children with Isolated Growth Hormone Deficiency**

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Background: Isolated growth hormone deficiency (IGHD) is a relatively common disorder. Current diagnostic protocols require a brain MRI of the hypothalamus and the hypophysis after establishment of the diagnosis, with the aim of identifying structural defects and specifically rule out an underlying space-occupying lesion. An MRI scan is costly and requires general anesthesia in young children. Data on the contribution of brain MRI in diagnosing children with IGHD are sparse.

Objectives: To examine the yield of brain MRI in the evaluation of children with IGHD and to define clinical and laboratory parameters that justify its performance.

Methods: A retrospective chart review of all children (<18 years) diagnosed with IGHD at two pediatric endocrinology units between 2008 and 2018 for auxologic, laboratory, and brain MRI findings.

Results: The study included 129 children (72 boys) with confirmed IGHD. The mean age at diagnosis was 7.5 ± 3.8 years (median 7.7 years, range 0.8–15.9). Boys were diagnosed at a younger age than girls (6.8 ± 3.7 vs. 8.5 ± 3.8 years, respectively, $p=0.02$). The mean height SDS at diagnosis was -2.2 ± 0.8 . The mean height deficit SDS (defined as the difference between height SDS at diagnosis and mid-parental height SDS) was -1.7 ± 0.9 . Five children (3.9%) had pathologic findings on their MRI: two had ectopic posterior hypophysis, two had hypoplastic hypophysis and one had Rathke cleft cyst. Six children (4.6%) had incidental findings of Chiari type 1 malformation. No space-occupying lesion was detected. The mean height deficit SDS among the children with pathological MRIs was -3.2 ± 1.4 vs. -1.6 ± 0.8 among the children with normal MRIs ($p=0.007$). Both a height deficit threshold of ≥ 2 SDS and a peak GH level threshold of $\leq 6.5 \mu\text{g/liter}$ identified all the pathological cases (sensitivity of 100% and specificity of 83%).

Conclusion: Our preliminary data indicate that most brain MRIs performed for routine evaluation of children with IGHD are not essential for establishing diagnosis. Only the children with extreme height deficit (≥ 2 SDS) and peak GH $\leq 6.5 \mu\text{g/liter}$ had pathological brain MRIs. Further studies with larger cohorts are needed in order to validate this revision of current protocols.

P1-398**Postoperative Quality of Life in Children and Adolescents with Craniopharyngioma – Results of the prospective multicenter trial KRANIOPHARYNGEOM 2007**

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Background: Craniopharyngioma is an embryonic tumor of low-grade malignancy. Children and adolescents with this diagnosis are analyzed concerning quality of life (QoL) and (progression-free) survival within the project KRANIOPHARYNGEOM 2007.

Methods: The prospective, multi-center project consists of a randomized, unblinded substudy with adaptive design and an observational study. The randomized substudy for incompletely resected patients compares direct postsurgical radiation with radiation at progression. Endpoint is self-assessment of QoL measured by PEDQOL. In explorative analyses, the influence of additional factors was analyzed using linear mixed models.

Results: In the interim analysis of the randomized substudy according to the intention-to-treat approach only marginal differences concerning QoL between the two treatment groups were observed ($n=24$). The explorative analyses ($n=131$) show that ant-/ and posterior preoperative hypothalamic involvement and postoperative hypothalamic lesions are associated with decreased QoL. After complete resection, the QoL is lower than with incomplete resection. Radiation, which is often performed due to progression after incomplete resection, is associated with reduced quality of life.

Conclusion: In order to achieve best QoL for children and adolescents with craniopharyngioma, hypothalamus-sparing therapeutic approaches are recommended. Based on the current data, it is not possible to recommend the optimal time for radiotherapy after incomplete resection with regard to QoL.

Pubertal events, reproductive and growth hormones and predictive factors in healthy girls with Transient Thelarche

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Context: Transient thelarche (TT) corresponds to the appearance, regression and subsequent reappearance of the breast bud in girls. Only a single study about its frequency and progression is available (Lindhardt Johansen JCEM 2017).

Objective and Hypotheses: To determine whether girls with TT girls (group 1) compared to girls without TT (group 2) show differences in i) timing/sequence of pubertal events ii) pattern of reproductive hormones and growth factors iii) genotype distribution of genetic polymorphisms associated with pubertal timing and iv) predictive factors (anthropometry since birth, maternal age at menarche).

Methods: The study population consist of the Chilean Growth and Obesity Cohort Study (GOCS, n=507 girls) followed since birth. Annual clinical examination including Tanner assessment until 1 yr postmenarche and fasting blood samples for metabolic, growth and reproductive hormones. Genotyping was performed by competitive and analysis was performed in STATA (version 14).

Results: In 7% (n=37) of the girls (n=507) TT was observed and in 65% of them breast development occurred below 8 years. Once progressive puberty, 51% started with pubarche in group 1 vs. 26% group 2, ($p<0.001$). During pubertal progression age at breast stage B2 (10.3 ± 1.1 vs. 9.2 ± 1.2 years, $p<0.001$) and menarche (12.3 ± 0.8 vs. 12.0 ± 1.0 years, $p<0.05$) were later in group 1. No differences in genotypes distribution of FSH β /FSHR nor in predictive factors were detected. Girls in group 1 who had the event below 8 years had lower DHEAS ($p<0.05$), Testosterone (T), Androstendione (A) and LH (all $p<0.005$) than girls with TT at older age. Girls in group 1 at the moment of puberty onset at breast Tanner 2 (B2) had higher DHEAS, IGF-1, LH, Insulin, estradiol, Testosterone and Androstendione (all $p<0.01$) than at TT. Comparison between group 1 and 2 girls during puberty onset at B2 showed lower DHEAS and IGF-1 ($p<0.005$), T, A, LH and estradiol (all $p<0.05$) and higher insulin ($p<0.001$) in group 1. Hormonal concentrations at B4 and 1 yr postmenarche did not differ.

Conclusion: Transient Thelarche appears to be a frequent event which does not appear to be mediated by hypothalamic-pituitary-gonadal axis activation, adiposity, peripheral conversion of androgens to estrogens, or genetic variations in FSH β /FSHR. These findings suggest that environmental exposure may play a role. We confirmed that TT girls entered puberty more frequently by the pubarche pathway and the subtle differences in hormonal levels at the initiation of puberty later disappeared, which indicates a benign nature of this condition.

Plasma Copeptin distribution in the pediatric age: A useful diagnostic tool for AVP-Related Disorders

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Introduction: Copeptin is a stable AVP surrogate, secreted in equimolar relationship, who has been proposed for the diagnosis of AVP-related hypo and hypernatremic disorders, i.e. the syndrome of inappropriate ADH secretions (SIADH), the cerebral/renal salt wasting syndrome (C/RSW) and diabetes insipidus (DI). Few data exist about the normal ranges for plasma copeptin levels in the pediatric age, reported between 2.4-8.6 pmol/L. The aim of this study is to represent the plasma copeptin distribution in a large pediatric cohort.

Methods: Plasma copeptin levels have been measured in 128 children and adolescents referred for other diseases than AVP-related disorders to the Department of Pediatric Endocrinology of Regina Margherita Children's Hospital in Turin in the period July 2016-May 2018. Plasma sample for copeptin analysis was collected early in the morning and the cohort was then splitted on the basis of recorded ingested fluid in the 6-8h before the sampling: Group A, with fluid fasting, Group B with free access to fluids.

Results: In the studied cohort plasma sodium level was 141.3 ± 1.63 in Group A (n=40) whereas in Group B (n=80) was 140.5 ± 1.81 ($p=0.02$). Significant difference was observed between the two groups also for plasma osmolality (285.6 ± 5.89 vs 283.5 ± 2.99 respectively, $p=0.008$). Mean plasma copeptin level was 6.76 ± 3.18 pmol/ (range 2-14.9 pmol/L). No difference was present among boys (n=42) and girls (n=86), displaying 6.96 ± 0.5 and 6.65 ± 0.34 values, respectively ($p=0.61$). Plasma copeptin levels in Group A were 10.26 ± 0.43 pmol/l, in Group B 5.16 ± 0.18 pmol/L ($p<0.001$). In all distribution percentiles copeptin levels were higher in children and adolescents with nocturnal liquid fasting (3rd percentile 3.42 vs 2.47 pmol/L; 5th percentile 3.9 vs 2.6 pmol/L; 10th percentile 5.94 vs 2.8 pmol/L; 25th percentile 8.73 vs 4 pmol/L; 50th percentile 10.6 vs 4.9 pmol/L; 75th percentile 12.3 vs 6.18 pmol/L; 90th percentile 13.84 vs 7.6 pmol/L; 95th percentile 14.3 vs 8.24 pmol/L; 97th percentile 14.76 vs 9.76 pmol/L).

Conclusion: Since plasma copeptin represents an emerging tool to investigate sodium and osmolality derangements, its evaluation should be included in the diagnostic flow-chart of AVP-related disorders. However, due to the extreme sensitivity of this parameter, in the interpretation of its levels, oral or intravenous administered fluids should be accurately considered.

P1-401**Management and treatment outcome of childhood-onset craniopharyngioma (CP) in Italy: multicentre collection of 117 cases**

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In Italy, treatment of children with CP is not centralized. We collected data of 117 patients (pts) (M/F 56/41) with CP diagnosed after 01/01/2000, followed-up in 14 centres of paediatric endocrinology belonging to the I.S.P.E.D. Five centres provided data on more than 10 pts (range 12-19), while the remaining on 1-9, 46 pts were diagnosed between 2000-2010 and 71 afterwards. Follow-up was 7.5 ± 4.1 yrs.

Results: Histology was adamantinomatous in 107 pts (91.4%), papillary in 6 pts (5.1%) and Rathke cyst in 4 (3.5%). The lesion was suprasellar in 92 pts (79%), involved the 3rd ventricle in 72 pts (61%). Age at intervention was 8.5 ± 4 yrs (1 mo-18.6 yrs), with 16 pts operated before age 4 yrs. Surgery was mainly performed in Florence (26 pts), Milan (18 pts), Rome (16 pts), Udine (11 pts) and Bologna (10 pts). Craniotomic surgery was chosen in 75 pts (64%), transsphenoidal in 39 pts (33%) (3 pts missing). In Bologna 8/10 pts were operated transsphenoidally, whereas in Florence (13t/13c), Rome (0t/16c), Milan (4t/18c) and Udine (2t/9c) transsphenoidal surgery ranged from 0 to 50 % of pts. Surgery changed over time (2000-2010 vs 2011-2018) with craniotomic approach declining, not significantly, from 76% (35/46) to 58% (56/71) with transsphenoidal surgery increasing from 20% (9/46) to 43% (30/71) ($p=0.01$). Complete resection remained stable, from 64% (29/46) to 55% (39/71) between the 2 periods. Post-surgery complications

occurred in 58 pts (50%) (8 pts missing) with Na electrolytes disorders in 19 pts followed by SAH in 12 pts and liquor fistula (7 cases). They were similar between those operated cranially (37/75; 49%) vs transsphenoidally (20/39, 51%). Radiotherapy was used in 40 pts: 10 pts underwent γ knife and 6 proton therapy. Recurrence occurred in 49 pts (42%): 1 in 30 pts, 2 in 15, 3 in 2, 4 in 1 and 6 in 1. In 98 pts hypothalamic syndrome was evaluated and occurred in 27 pts (27.5%). 9 pts also developed severe obesity (BMI > 2 SDS): this group (27+9 pts) had either craniotomic (26/64, 41%) or transsphenoidal surgery (10/34, 29%) ($p=ns$).

Conclusion: Our children with craniopharyngioma were diagnosed and treated at all ages in several centres around the country. The proportion of pts undergoing craniotomic vs transsphenoidal surgery varied significantly among the various centres. We confirm that recurrence occurred in about 40% of pts and hypothalamic disturbances in more than 1/3 of pts irrespective of type of surgery.

P1-402**Evaluation of brain MRI lesions in 381 girls with central precocious puberty**

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Central precocious puberty (CPP) in girls is a diagnosis increasingly made by the Pediatric Endocrinologists worldwide. Although it is most frequently of idiopathic origin, magnetic resonance imaging (MRI) of the brain is recommended to rule out organic lesions causing CPP. However, controversy exists regarding the age limits for routinely performing MRI in girls with CPP. Objective: To evaluate the outcome of brain MRI in girls diagnosed with CPP and its relationship with age and clinical and biochemical parameters. Method: A single-center, study of 381 girls with CPP who had brain imaging performed between 2008-2018. The results of imaging were categorised as Group 1:Normal, Group 2: incidental CNS lesions, Group 3: previously known CNS lesions Group 4: newly identified CNS lesions. Clinical and biochemical features of four groups were compared. Additionally, MRI lesion frequency was determined based on three age categories (<6 y, 6-8, >8 years) Results: MRI findings were abnormal in 73 patients (19%). 18 girls (4.7%) had well known brain pathologies at the time of referral. In the remaining 363 girls with CPP, who had no CNS symptoms, MRI revealed CNS abnormalities in 55 girls. In 34 girls (8.9%) MRI findings were considered as incidental findings, which were not related to the early puberty. Another 21 girls (5.5%) had newly identified MRI abnormalities which were considered to be causally related to CPP. Among these, 19 lesions were non-neoplastic and included arachnoid cysts (6) pineal cysts (4) hydrocephaly (2) Chiari Type2 malformation (1) Dandy-Walker malformation(1) and others (5) not requiring surgical intervention during follow-up. There were only 2 tumoral lesions (0.5%) in the cohort (1 hamartoma and 1 glioma) and they required

surgical intervention. These two cases were the youngest of the entire cohort (1.0 and 2.7 years of age respectively) and had the highest baseline LH and Estradiol levels. Otherwise, clinical and biochemical parameters were similar in 4 groups. Newly identified CNS lesions were detected throughout all ages including those above 8 years (Table). Conclusion: Although CNS lesions can be detected throughout all age categories in girls with CPP, only 5.5 % are causally related and most of them do not require intervention. CPP due to neoplastic lesions are detected in younger patients who also had a robust activation of pituitary-gonadal axis.

P1-403

Xanthomatous hypophysitis : a rare case in a paediatric patient

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Background: Hypophysitis is a rare inflammatory condition of the pituitary that can mimic a neoplastic lesion. Histopathology subtypes include lymphocytic, granulomatous, xanthomatous, plasmacytic or a mixed picture. Among these, xanthomatous hypophysitis (XH) is the least common with an unknown aetiology. Unlike lymphocytic hypophysitis, which is believed to be autoimmune in origin, XH is rarely reported to be associated with other autoimmune diseases and response to glucocorticoid is less clear.

Case Report: We present a girl with XH who was referred for stunted growth and delayed puberty at the age of 14 years. On examination, she was short at 120cm (>2 SD below her mid-parental height) and pre-pubertal. Neurological and visual fields examination were normal. She had multiple pituitary deficiencies (growth hormone, TSH, gonadotrophins) and four years later developed diabetes insipidus. However, she did not develop adrenal deficiency. This was also similar with other cases of XH whereby adrenal deficiency is reported to be less common.

Her first MRI in January 2013 revealed a homogenous lobulated mass, measuring 0.6x1.3x1.7 (APxWxCC) arising from the pituitary stalk with extension to the sellar, suprasellar regions, and abutting the optic chiasm. Autoimmune, infectious and secondary workup for tumor including germinoma was negative. Repeated MRI did not show a change in mass size until three years later there was an increment measuring 1.8x 1.4x1.0 cm (APxWxCC). She then underwent a partial resection for diagnostic and therapeutic purposes. A complete resection was not done due to the location and nature of the tumor. Histopathology was suggestive of XH.

Post-resection MRI over a two-year period showed a continued gradual increment of mass size measuring 2.1x1.2x1.6 cm (APx-WxCC). After a multi-disciplinary consultation, a decision was made for a trial of steroids. Oral prednisolone 30mg (1mg/kg) once daily was administered for 2 months and tapered off weekly. Repeated MRI six months after completion of prednisolone 1mg/kg/day showed a smaller mass measuring 1.2x1.0x1.4 cm (APx-WxCC). While there was still superior displacement of the optic chiasm, her visual acuity and visual fields remained normal.

Conclusion: We report a girl with XH post-surgical resection with a residual progressive lesion that showed a response to glucocorticoid with no acute side effects. While glucocorticoid could

be a treatment option for selected cases of XH, there is insufficient evidence to recommend its routine use as well as the best regimen and timing; in addition, understanding of the pathogenesis, progression and prognosis of the disease remains limited.

P1-404

Improvement of final height in idiopathic central precocious puberty is associated with delay of bone maturation with GnRH agonist therapy under the age of 7 years

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Background: GnRHa therapy is shown to be beneficial in increasing final height when started before 6 years of age in girls with idiopathic CPP(iCPP). However controversial data exist in improvement of final height whose pubertal signs appear after age of 6.

Aim: To investigate effect of age of onset of GnRHa therapy on final height n girls with iCPP, and to evaluate factors affecting height gain.

Methods: Eighty-four girls with iCPP who were treated with GnRHa and had reached final height were included.These cases were grouped as <6yrs, 6-6.9yrs, 7-7.9yrs, ≥8yrs according to age of initiation of therapy.Final heights of these cases were compared with data of 18 girls with CPP who refused therapy.Height gain was defined as difference between final height and predicted adult height(PAH) at start of therapy.Rate of bone age maturation was calculated by dividing difference between bone ages at the end and beginning of therapy by duration of therapy.

Results: There was no significant difference in terms of height gain between patients who started GnRHa therapy after 8 years of age and those who were not treated(5.9 ± 4.2 cm vs 5.7 ± 4.0 cm) ($p:0.852$). Height gain of those who started GnRH before age of 8 was significantly higher than not treated group(9.5 ± 5.8 cm vs 5.7 ± 4.0 cm) ($p<0.001$). Results:showed that height gain was significantly increased as age decreased(<6yrs 13.3 ± 6.1 cm, 6-6.9yrs 9.8 ± 5.8 cm, 7-7.9yrs 6.6 ± 4.9 cm)($p:<0.001$). Height gain after end of therapy until final height was significantly higher in cases who were treated at an early age(<6yrs 10.2 ± 6.1 cm, 6-6.9yrs 7.1 ± 5.9 cm, 7-7.9yrs 5.6 ± 3.9 cm, ≥8yrs 4.0 ± 2.9)($p<0.001$). Rate of bone age maturation according to age groups were found as 0.6 ± 0.2 for <6 yrs of age, 0.6 ± 0.2 for 6-6.9yrs, 0.8 ± 0.3 for 7-7.9yrs, 0.9 ± 0.4 for ≥8yrs($p<0.001$). Pace of bone age advancement was reduced more effectively in those whose therapy started at a younger age. In multivariate linear analysis, most important factors affecting height gain were age of initiation of therapy and target height-SDS.

Conclusion: GnRHa therapy has a positive effect on final height in girls with iCPP whose therapy was started before 8 years of age. This effect becomes more significant as age of initiation of therapy decreases before 7 years of age.Reduction of bone age advancement results in increase in height gain after end of therapy till final height. After 8 years of age, contribution of GnRHa therapy to final height is controversial.

P1-405

Metabolic changes in children treated for medulloblastoma

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The development of endocrine disorders after complex treatment of medulloblastoma is out of doubt. Much less attention is paid to the study of metabolic changes in the outcome of treatment. In our clinic, we examined 63 patients (40 males/23 females) after the complex therapy of medulloblastoma (surgery, craniospinal radiation therapy and chemotherapy). Patients had a median age (range) of 11.3 (5.5–17.9) years. They were treated for medulloblastoma when aged 6.8 (1.2–16.2) years. The median time after the end of treatment was 3.7 (1.5–11.6) years. Overweight (SDS BMI >1) was observed only in 16 patients (3 girls and 13 boys), obesity (SDS BMI >2) in 1 boy. Dyslipidemia was found in 34 patients (54%). All patients underwent oral glucose tolerance test. Insulin resistance (ISI Matsuda <2.5, HOMA-IR >3.2) was detected in 7 patients, impaired glucose tolerance (120 min glucose ≥7.8 mmol/l) was observed in 2 patients with IR and in 2 patients without IR. At the same time, IR and impaired glucose tolerance were encountered in only 5 children with overweight and no one with obesity. All patients with impaired glucose tolerance had normal values of fasting glucose (4.3 ± 5.04 mmol/l) and HbA1c (4.8 ± 5.8%). A bioelectrical impedanciometer was used to measure body composition in 49 cases, the percentage of adipose tissue was increased in 14 patients (28%) with normal BMI (<1). Resting metabolic rate (RMR) was calculated using indirect calorimetry, with a gas exchange analyzer to measure oxygen use and carbon dioxide production. In 25 patients there was normal RMR, in 16 there was low RMR, and 7 patients had high RMR. We compared the basal metabolic rate before the start of growth hormone therapy and 6–12 months after. In 6 patients, no significant changes were detected.

In our group of patients after complex therapy for medulloblastoma metabolic changes, such as dyslipidemia were observed in 54 percent of children (34/63). Insulin resistance and impaired glucose tolerance, were found in 14 percent of children (9/63), while 74 percent of patients had a normal or low body mass index. In this group of patients, it is necessary to conduct careful follow up including oral glucose tolerance test and measure of body composition.

P1-406

Tolvaptan for management of intractable salt and water imbalance in a case with suprasellar tumor after surgery

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Background: It is sometimes difficult to diagnose and manage fluid and electrolyte imbalance after surgery for hypothalamic/pituitary tumors. We present a pediatric case of severe SIADH successfully treated with tolvaptan after suprasellar tumor resection.

Case: The case was 8-year-old girl with growth failure. She was found to have suprasellar tumor on CT scan when she accidentally fell down and hit her head. MRI suggested a craniopharyngioma. There were no abnormalities in water and electrolyte balance or hormonal data before surgery. Tumor resection by craniotomy was performed and diabetes insipidus was recognized 12 hours after the operation and treated with DDAVP. Serum sodium level gradually decrease to 130 mEq/l without dehydration from the 4th postoperative day (POD) and SIADH was suspected. Water restriction was started but hyponatremia decreased to 126 mEq/l with increasing urinary Na+. Dehydration was also noticed on 6th POD, thus 3% saline infusion and intravenous fluids were started with the diagnosis of combined cerebral salt wasting (CSW). The sodium level further decreased to 117 mEq/L. The continuous hypertonic saline and fludrocortisone administration did not improve hyponatremia. We started treatment for SIADH using tolvaptan on POD 8. Three hours after start of tolvaptan administration, serum sodium level increased to 125 mEq/L. Hypotonic polyuria was observed after tolvaptan treatment stopped. CDI was observed afterwards.

Discussion: Triphasic response is known to occur after hypothalamic and pituitary tumor resection. The second phase of SIADH, the duration and severity of this phase is variable and may last from 2 to 14 days. CSW is thought to be an independent phase or extreme condition of SIADH. In this case, it was difficult to diagnose whether the patient had either CSW or SIADH in the postoperative acute phase. The use of tolvaptan promotes free water excretion and may have suppressed the progression of hyponatremia, but it may have been used at the timing of entering DI.

Conclusion: Tolvaptan which is sodium sparing diuretics should be considered in children's severe SIADH with progressive hyponatremia that does not improve with water restriction and sodium load.

P1-407**No association between serum level of NPTX 1 and MKRN3 in central precocious puberty**

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Background: Makorin ring finger protein 3 (MKRN3) is most common genetic cause of central precocious puberty (CPP) and associated with the initiation of puberty. Although its actual function is veiled. Recent study reported MKRN3 interacted with and suppressed neural pentraxin-1 precursor (NPTX1) activity via polyubiquitination during early puberty in mice.

Objective: The aim of this study was to investigate the correlation between serum NPTX 1 and MKRN3 in CPP girls.

Methods: In this case-control study, we examined 38 girls referred for early breast development (before the age of 8 years). The control group included healthy and prepubertal girls. Anthropometric and hormonal parameters were measured and serum level of NPTX1 and MKRN3 were evaluated by commercial ELISA kit.

Results: Serum MKRN3 level was significantly higher in CPP patients than controls($p < 0.001$). In patients, serum NPTX1 level was measured higher than control, there was no statistical difference ($p = 0.228$). Also, serum NPTX 1 was positively correlated with peak LH ($r = 0.338$, $p < 0.05$), there was no correlated between NPTX1 and MKRN3 in CPP girls($p = 0.882$).

Conclusion: Serum MKRN3 decrease and NPTX1 tends to increase in CPP girls. Although, serum NPTX1 and MKRN3 have no significant association, they are likely to be involved in the onset and regulation of puberty.

P1-408**Training in pubertal assessment – First step to the observational pilot study PROSPEL (Premier Observatoire des Stades Pubertaires en Libéral)**

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Introduction: Recent publications report an earlier age of onset of pubertal changes in the US and Europe. Referrals to pediatric-endocrinologist for early puberty are increasing. Precocious puberty diagnosis is often delayed, especially in boys. Improvement in pubertal assessment (age at onset of puberty) by pediatricians and general practitioners is needed to participate in the PROSPEL study and to improve management of pubertal abnormalities.

Materials and Methods: Private physicians were recruited in Bordeaux and Toulouse to participate in a training session on practical modalities for assessing pubertal stages according to Tanner's

classification. Slides showed breast development and pubic hair. An orchidometer was distributed to each participant for testicular volume estimation. The post-intervention assessment included a test administered on their mobile phone via the Kahoot application and "blind" palpation of orchidometer beads. Intra-individual reproducibility was analyzed by repeatedly presenting the same orchidometer element. Inter-individual reproductibility was assessed by a double examination of a number of children.

Results: Sixty-three physicians participated in the study (35 pediatricians and 28 general practitioners), where 87.5% distinguished a prepubescent child from a pubescent with the slide test, and 80% with the blind palpation test. Intra-individual reproducibility showed a weak agreement. Inter-individual reproductibility was excellent. In the PROSPEL preliminary feasibility study, all the physicians were certified at the end of the training session. During a 4 weeks period, 2646 children (1318 girls - 1328 boys) were included, in a homogeneous age distribution. The study was carried out in 83.5% of cases.

Discussion and Conclusion: Our results validate our training methodology and certification process for participating physicians in the PROSPEL study.

Sex Differentiation, Gonads and Gynaecology or Sex Endocrinology

P1-409**Long-term outcome in young women treated for central precocious puberty**

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Background: GnRH-analogs (GnRHa) are the recommended treatment for Central Precocious Puberty (CPP). Despite a normal long-term outcome is generally reported, reproductive function and emotional sphere in adulthood are still poorly evaluated.

Objective: To evaluate the general long-term outcome of young women with previous CPP treated with GnRHa.

Patients and Methods: A cohort of 63 young women (25.5 ± 5.31 years) with history of CPP treated with GnRHa were enrolled.

All subjects received diagnosis of CPP at a men age of 7.01 ± 1.35 years, and were treated for 2.02 ± 1.43 years. Mean chronological age and bone age (BA) at the end of treatment were 10.15 ± 0.87 and 12.1 ± 0.86 years respectively. Menarche occurred 15.5 ± 9.59 months (range 2-43) after treatment was discontinued.

At the enrolment all subjects underwent the following evaluations: gynecologic and menstrual cycle pattern history; anthropometric measurements and physical examination including signs of hyperandrogenism; pelvic US; Female Sexual Function Index (FSFI) questionnaire to investigate sexual and emotional sphere.

Results: Adult height (AH) (158.4 ± 6.3 cm) was within the genetic target (158.1 ± 4.7 cm) and significantly higher than predicted stature at diagnosis (155 ± 5.4 cm; $p=0.0001$).

Mean height gain (+3.1 cm) was negatively correlated with BA at the end of treatment ($r: -0.3684$; $p=0.0035$) and with uterine length at diagnosis ($r: -0.29$; $p=0.025$).

Height gain was higher in patients treated under 6 years (+4.3 cm) compared to those treated between 6-8 years (+2.0 cm, $p < 0.0001$).

Overweight/obesity was detected in 36.5% of patients at diagnosis and increased up to 46% during treatment; however in adult age only 30.2% of subjects were overweight/obese.

Gynecologic history revealed that 34.1% had menstrual irregularities and 27.3% received diagnosis of PCOS.

Assessment of emotional and sexual sphere revealed dyspareunia in 100%, difficulties in reaching orgasm in 60%.

Only 10% of patients planned pregnancy (due to young age of most women) and none of them reported fertility problems.

Conclusions: Our study confirms that AH is normal in girls with CPP treated with GnRHa and that height gain is higher in patients treated before the age of 6 years.

An increase in BMI is observed during treatment, but this effect seems to be transient, with no increased risk of overweight/obesity in adulthood.

We observed an increased prevalence of PCOS compared to general population, and problems in affective-sexual sphere. Whether these findings are intrinsic to CPP *per se* or to GnRHa therapy require further studies.

Objective: To assess function of the pituitary-testicular axis, with emphasis on Sertoli cell function, in boys and adolescents who received chemotherapy for hematologic malignancies.

Methods: We performed a retrospective analysis including 97 patients (58 treated before age 10 yr and 39 treated between 10 and 18 yr), 83 with acute lymphocytic leukaemia (ALL), 5 with acute myeloid leukemia (AML) and 9 with non-Hodgkin lymphoma (NHL). Serum LH, FSH, testosterone and AMH (as a direct marker of Sertoli cell function) were used as endpoints.

Results: Cross-sectional analysis included 61 patients with one AMH measurement between 1 to 8 years after the end of treatment. 37 were treated before age 10 yrs and evaluated at 9.4 yrs (5.7-14.9). No patient had AMH <2 SDS. One (2.7%) patient had LH >2 SDS and 3 (8.1%) had FSH >2 SDS. Twenty-four patients were treated after age 10 and evaluated at 15.3 yrs (11.6-20.1). No patient had AMH <2 SDS. Five (20.8%) patients had LH >2 SDS and 8 (33.3%) had FSH >2 SDS. No patient had testosterone <2 SDS.

All 97 patients were included in the **longitudinal analysis**. During follow up 3/58 (5.2%) patients treated <10 yrs had at least one AMH <1 SDS, but none had AMH <2 SDS. Nine (15.5%) had FSH >2 SDS and 4 (6.9%) had LH >2 SDS. Of patients treated at an age >10 yrs, 10/39 (25.6%) had at least one AMH <1 SDS, but none had AMH <2 SDS. Fourteen (35.9%) had FSH >2 SDS and 11 (28.2%) had LH >2 SDS. The proportion of patients with LH and FSH >2 SDS was higher in the group of patients treated at >10 yrs ($p:0.03$ and 0.008 respectively).

Conclusion: Sertoli cell function is not affected by chemotherapy in boys with hematologic malignancies. During follow up high gonadotrophins are more prevalent in boys treated at pubertal age. In some patients, high FSH may be due to germ cell damage and high LH with normal testosterone may reflect a compensated Leydig dysfunction.

P1-410

Sertoli cell function after chemotherapy in boys with hematologic malignancies

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Introduction: Gonadotoxicity associated with chemotherapy of hematologic malignancies has been described mainly in adults, focused on the sensitivity of germ cells. Little attention has been placed on Sertoli cells during childhood and puberty, even though Sertoli cell development is essential for adult spermatogenesis.

P1-411

Gender decision in disorders of sex development (DSD) patients: 20 years' experience

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Gender uncertainty is stressful condition for children and their families. Gender assignment in children with disorder of sex development (DSD) is considered as a medical emergency. Influencing factors to consider when debating gender assignment include medical diagnosis, external genital appearance, potential of fertility and sexual, therapeutic and/or surgical intervention options, views and desires of patients and families, situation of social-cultural factors, the psychological gender development status of child.

The purpose of this study was to investigate the results of gender assignment in children with DSD in our clinic. The file records of the DSD council between years 1999-2019 were reviewed.

The mean age of the total 209 patients with DSD at the time of first admission were 3.1 (\pm 4.7) years. Of the 209 patients, 130 had gender uncertainty, 18 had adrenal crisis, 22 had swelling in the groin, 15 had no testes, 18 were primary amenorrhea, 4 had gender uncertainty history in family, 2 had micropenis, 1 had short stature, and 1 had absence of vaginal meatus. With regard to the Chicago Consensus, 87 patients were 46,XX DSD, 110 were 46,XY DSD and 12 were sex chromosome DSD. Congenital adrenal hyperplasia was the most common etiological cause of DSD. The mean age of patients at the time of decision consensus meeting were 4.5 (\pm 5) years. In psychological evaluation, it was determined that 82 of the patients were in compliance with the female gender, 50 were in compliance with the male gender, and 77 patients were not yet any gendered. We observed that parents raised 129 children as girl, and 80 children as boy. In 46,XX patients, 77 of 87 (88.5%) were decided to be supported in as girl gender, 5 of as boy, and 5 with followed up. In 46,XY patients, 40 of 110 (36.4%) were decided to be supported in as girl gender, 67 of as boy (61%). In sex chromosome DSD patients, 3 of 12 were decided to be supported in as girl, 9 of as boy.

We present about 20 years of experience in DSD gender assignment. Gender assignment in DSD patients is a difficult situation both for the patient's family and the physician. Many factors should be considered. And these decisions should be taken by an experienced council.

P1-412

WES analysis of a cohort of 94 patients presenting with 46,XY and 46,XX DSD

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Background: Disorders/Differences of Sex Development (DSD) is diagnosed in approximately one out of 4'500 newborns. Children born with DSD present with a very diverse phenotype and they and their families face considerable challenges, potentially including surgical intervention and gender assignment, as well as associated complications such as infertility and predisposition to gonadal tumors. Due to the lack of knowledge concerning the complete gene and protein pathways involved in sex development and DSD, causative genetic variants currently can only be identified in about 50% of the affected patients.

Methods: Whole exome sequencing (WES) was performed on a large cohort of 96 46,XY and 46,XX DSD patients in order to identify new genes and variants implicated in DSD. By applying different filtering methods, variants in known DSD genes as well as variants in new genes potentially causative for DSD, were identified.

Results: For 26 patients, causative genetic variants in previously known DSD genes could be identified. Additionally, 40 new potential candidate genes for DSD were identified based on the

number of patients carrying variants, the similarity of the phenotype, the pathogenicity prediction and their expression in tissues important for sex development (e.g. gonads and pituitary), like CCDC88C.

Conclusion: WES is an important tool that allows for the identification of new genes potentially involved in DSD, advancing our understanding of human sex development and our capacity to accurately diagnose, support and treat patients and their families.

P1-413

Assessment of the Function of Lower Urinary Tract Following Feminizing Genitoplasty in Females with Congenital Adrenal Hyperplasia

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Introduction: In virilized females with Congenital Adrenal Hyperplasia (CAH), the principal aims of surgery are to reduce the size of clitoris, create a vaginal orifice that will allow menstrual flow and intercourse, and to correct the urogenital sinus to prevent incontinence.

Surgical techniques evolved with time to make not only "cosmetically accepted" genitalia but also normally functioning. The complications of feminizing genitoplasty include urinary complications as regards the voiding function and continence.

Symptoms of voiding dysfunction include dysuria, urgency, and frequency. The dysfunctional voiding scoring system may help to identify patients with postoperative urinary complications.

Aim of the work: To assess the function of lower urinary tract following Feminizing Genitoplasty in females with CAH.

Subjects and Methods: This study included 40 female children with CAH aged more than 3 years attending the endocrinology clinic in Alexandria University Children's Hospital, Egypt. Thorough history taking and clinical examination were done with emphasis on age at diagnosis and duration of disease, timing and stages of surgery, and presence of urinary symptoms. Assessment of lower urinary tract function using dysfunctional voiding score system was done for them at least 6 months after the surgery. Urodynamic evaluation was performed for females with score more than 6.

Results: The mean age of the cases was 8.2 years with mean duration of CAH of 7.9 years. 67.5% were controlled on medical treatment and 80% had done surgical correction in one stage operation. By applying the dysfunctional voiding score system, 72.5% of cases had score \leq 6 and there were 11 cases (27.5) had score $>$ 6. It was found that 7 cases (out of 11 with high score) had Bell shaped curve on Urodynamic study. There were 3 cases with Interrupted curve and only one case with Plateau curve. There were 9 patients improved after toilet training.

Conclusion: Lower urinary tract symptoms are common in females children with CAH after Feminizing Genitoplasty so early assessment is needed to prevent urinary complications.

P1-414**Gonadal Insufficiency and Affecting Factors in Patients with Bone Marrow Transplantation(BMT) for Non-malignant Indications in Childhood or Adolescence**

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Introduction: Gonadal insufficiency is a common long-term endocrinological complication of BMT and is mainly associated with the chemotherapy protocol. In the literature, gonadal insufficiency after BMT varies between 66% -80% in girls and 35-60% in boys

Aim: to investigate the frequency and the factors affecting gonadal insufficiency in cases with BMT due to non-malignant indications in children or adolescence.

Methods: Between 39 BMT patients were included in the study. Patients were classified according to diagnosis, treatment protocols, age during chemotherapy and their effect on gonadal insufficiency were investigated. Gonadal insufficiency was defined as inappropriately high gonadotropin levels for the pubertal stage. Those who had gonadal insufficiency before BMT or had any other treatment that could cause gonadal insufficiency and those with chromosomal abnormalities were excluded from the study.

Results: Of the 39 patients, 20 were female (51.3%) and 19 (49.3%) were male. The median age at admission was 10.73 years (2.82-18.75) and the age of BMT was 8.16 years (0.57-17.01). In terms of diagnosis, 11 (28.2%) had thalassemia major, 9 (23.1%) Fanconi aplastic anemia, 6 (15.4%) aplastic anemia, 3 (7.7%) severe combined immunodeficiency, 3 (7.7%) chronic granulomatous disease, 2 (5.1%) hyper IgM syndrome, 2 (5.1%) hyper IgE syndrome, 1 (2.6%) metachromatic leukodystrophy, 1 (2.6%) Wiskott Aldrich syndrome 1 (2.6%) Diamond Blackfan anemia.

Hypergonadotropic hypogonadism (HH) after BMT was detected in 13 (33%) of the patients. Median age of the patients with and without gonadal insufficiency was 11.23 years (5.56-16.11) and 6.88 years (0.57-17.01) respectively ($p = 0.031$). 12 (92 %) of these patients were prepubertal whereas 1 of them was at Tanner stage 2.

Patients with gonadal insufficiency received at least two out of Fludarabine, Cyclophosphamide or Busulfan regimens. Although 4 (80%) of 5 patients who received Fludarabine-Busulfan-Cyclophosphamide BMT regimen had gonadal insufficiency, none of the 5 patients receiving cyclophosphamide had gonadal insufficiency. Conclusion: In the indications of BMT, non-malignant causes are increasing for years and treatment protocols are changing. Gonadal insufficiency was found to be lower in this study compared to the literature. BMT in prepubertal phase, advanced age and the presence of at least two of Fludarabine, Cyclophosphamide or Busulfan regimens in pre-BMT period are risk factors.

P1-415**Clinical and Molecular Characteristics of Russian Patients with 46,XY DSD due to NR5A1 Gene Mutations**

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Background: Steroidogenic factor 1 (encoded by the NR5A1 gene) is a transcriptional regulator of genes involved in gonadal development and steroidogenesis. Mutations in NR5A1 have been identified among the most frequently genetic causes of disorders of sex development (DSD).

Objective: To report the phenotype of 31 patients associated with 17 novel and 9 previously described NR5A1 sequence variants identified in Russian patients with 46,XY DSD.

Method: Targeted next generation sequencing (NGS) analysis with a panel of 43 genes associated with sex development was performed in 280 patients with DSD 46,XY.

Results: Among 280 patients with 46,XY DSD NR5A1 variants were found in 31 patients (11%). We identified 28 pathogenic variants, including 17 novel and 11 previously reported. 27 patients presented with abnormal genitalia at birth, 7 of whom had only slightly enlarged clitoris and gonads in labia majora. 11 patients were assigned at birth as males. 3 patients with completely female external genitalia at birth were diagnosed at puberty due to profound masculinization. None of them had Mullerian derivatives. The previously described NR5A1 allelic variants c.102+1G>T and R313C were identified in two of them and a novel H24Q mutation was found in the third one. The mutation R313C was also found in the other three patients with severe undervirilized external genitalia (EMS 3-5). Only 1 of the patients showed transient adrenal insufficiency during infancy. Four of our patients, who were registered as males went through puberty with normal spontaneous virilization, adequate testes volume and penile enlargement. Two of them (age 14 and 15 y) at present have gonadotropin levels within normal range, and the other two (21 y and 25 y) showed slightly elevated FSH level, upper normal level of LH and lower normal level of testosterone. DNA analysis in these 4 cases showed 2 previously described (R84H and R313H) and 2 novel (G321V and c.951delC) variants in NR5A1 gene. Among 20 patients with female assignment at birth 18 underwent bilateral gonadectomy and in 2 cases gonads were left for the follow-up. During laparoscopic procedure Mullerian derivates were found in four patients. Most our patients are still in prepubertal age and will be followed further.

Conclusion: Mutations in NR5A1 gene were found in 11% cases of 46 XY DSD and 17 novel pathogenic variants were identified in our cohort. Our results contribute to the better understanding of diverse phenotypes associated with alterations in the NR5A1 gene.

Creating a clinical evaluation system for simple and comprehensive scoring of differences/disorders of sexual development

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Background: The Prader and Quigley classifications (P/Q-C), used widely to evaluate external/internal genitalia in differences/disorders of sexual development (DSD) patients, are sometimes unsuitable for determining the stage/grade because they were originally designed to assess 46,XX 21-hydroxylase deficiency (21OHD) and 46,XY androgen receptor defects (ARD), respectively. The external masculinization score (EMS) is also used to assess masculinization of the external genitalia in 46,XY DSD.

Aim: To create a simpler, more comprehensive DSD scoring system.

Methods: Our scoring system (DSD scoring system; DSD-SS) was developed to assess all DSD types in neonates and infants irrespective of gender assignment and consists of six items pertaining to the external/internal genitalia and gonads, including a) growth and fusion of scrotum/labia majora, b) glans penis development, c) urethral orifice position, d) presence or absence of the urogenital sinus, e) presence or absence of the uterus, and f) gonadal position (scrotal, inguinal, or abdominal). Each item has two to four ranks (for a score of 0 to 6), with the normal male pattern having the highest score. The DSD-SS was validated as follows: photographs of eight DSD patients illustrating conditions a), b), and c) above were scored by 45 physicians with zero to over 20 years of experience with DSD. Then, the differences in their scores were assessed. Next, the results of the DSD-SS were compared with those of the P/Q-C and EMS using photographs and medical records of patients with 21OHD, ARD, and 45,X/46,XY. Finally, two authors compared the scores for four DSD patients based on direct physical examination and photographs.

Results: No inter-observer variation was found, except in the items pertaining to scrotal/labia majora growth and the glans penis. 45,X/46,XY patients with the same P/Q-C grade had quite similar scores using the DSD-SS. In addition, 45,X/46,XY patients who were unable to be classified in one specific stage/grade by the P/Q-C were able to be classified using the DSD-SS. Assessment of the degree of virilization in 21OHD, ARD, and 45,X/46,XY patients using the DSD-SS corresponded to the results of the P/Q-C. The EMS and the sum of the new scores for external genitalia correlated in seven cases of 45,X/46,XY. A close correspondence in scores based on a direct physical examination or photographs was also seen.

Conclusion: The new DSD scoring system enabled simple and comprehensive evaluation of fetal sex development.

This is a side-by-side submission with the presentation by Kawai et al. (submission No. 669).

Hypospadias: clinical approach, surgical technique and outcome. Twenty years' experience of a single centre

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Background: Hypospadias is one of the most common congenital abnormalities in male. Nowadays, hypospadias surgical repair has become highly demanding and deeply investigated with more than 300 corrective procedures. Its success is assessed by the "reoperation rate" that occurs short after the surgery within a brief follow-up (6-12 months). However, short-term outcomes may not reflect the long-term ones, as hypospadias repair may influence adolescence and adult life. This study aims to identify the cosmetic, functional and psychosexual outcomes on a long-term follow-up and to suggest an innovative approach to the hypospadiac patient's care, as well as providing a review of a singol center experience.

Methods: Medical records of 398 patients treated by the same surgeon for hypospadias between August 2001 and December 2017 were reviewed. Families were reached by phone and invited to attend a free-charge follow-up examination. A life-related interview and 3 validated questionnaires (the Penile Perception Score-PPS, the Hypospadias Objective Score Evaluation-HOSE, the International Index of Erectile Function-5-IIEF5) were used, according to the age, to compare the parents', patients' and surgeon's opinion on long-term outcomes.

Results: 187 patients were included in the study (response rate 47%). 46 patients (24.6%) presented at least one complication after the repair with a mean elapsed time of 17.6 months (SD 18.96). Longitudinal differences in surgical corrective procedures ($p<0.01$), clinical approach ($p<0.01$) and hospitalisation after surgery ($p<0.01$) were found. Cosmetic data from the PPS were similar among patients and parents, with no significant differences according to patients' age nor to the type of hypospadias: 83% of the patients and 87% of the parents were satisfied with the cosmetic result. A significant difference in functional outcome relating to the type of hypospadias was reflected by the HOSE among patients ($p<0.001$), parents ($p=0.02$) and surgeon ($p<0.01$). Patients' HOSE total score was consistently lower compared to the surgeon one ($p<0.01$). The HOSE satisfaction rate on functional outcome was 89% for patients and 92% for parents. No data were available from the IIEF5 questionnaire.

Conclusion: Long-term hypospadias outcomes still represent a debated issue for scientific community and a standardized approach to evaluate the consequences of surgery through time is needed. We propose an innovative algorithm in attempt to fill the gap of the present literature.

Epidemiology of diagnoses of Sex Development Disorders based on the Registry of rare diseases, in a large area of North-Eastern Italy

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Background: Disorders of Sex Development (DSD) are a rare disease often caused by complex genetic mechanisms, with a wide spectrum of clinical manifestations that lead to a continuous evolution of the diagnostic classification. From 2002, In the Veneto Region, all DSD diagnoses have been collected thanks to the creation of a Registry for Rare diseases, including DSD.

Material and Methods: We could retrospectively analyze the etiology distribution of the DSD diagnosed by the Pediatric Endocrinology Unit of University of Padua, which most patients of a large area of the North-Eastern Italy refer to. To analyze the time trend of diagnosis, we considered 3 periods: before 2002, from 2002 to 2009 and from 2010 to 2018. Moreover, we reviewed outpatients' data to obtain the type of diagnosis, the date and the age at diagnosis. DSD were classified following 2005 Chicago Consensus Conference.

Results: in the whole reviewing Registry data we counted 374 new DSD diagnoses. Outpatients' data from 147/374 were obtained. Among them, the distribution of DSD diagnosis was as follows: 58 Sex Chromosome DSD, 34 46,XY DSD and 55 46,XX DSD. In 104 patients, age at diagnosis was available. The median age at diagnosis resulted significantly higher in patients diagnosed between 2010 and 2018 in comparison with the other two periods ($p=0.003$), with an higher, albeit not significant, frequency of 46, XY DSD diagnosis. Indeed, among the 28 patients with 46, XY DSD in which the date of diagnosis was available, 7% were diagnosed before 2002, 25% between 2002 and 2009 and 66% between 2010 and 2018. The median age at diagnosis was significantly higher in patients diagnosed after 2002 (85%) in comparison to patients diagnosed before 2002 (16%) ($p=0.02$).

Conclusion: Our analysis showed a trend towards an increase in the total number of DSD diagnoses over the years. With the limit represented by a lack of a Registry, before 2002 nearly all the diagnosis were made at birth, by the evidence of ambiguous genitalia, coming mostly from classical CAH (50%) and Sex Chromosome DSD (35%). We observed a trend towards an higher age at diagnosis in the 2010-2018 period, with an increased in 46,XY DSD diagnosis. We suggest that this different distribution may be due to a progressively wider use of prenatal chromosomal sex determination and a better management of the early adolescence clinical signs by the Pediatric Endocrinologists. The ongoing study of all our patient's data could better define these hypotheses.

Premature ovarian insufficiency in women after treatment for childhood cancer is a risk factor for metabolic syndrome

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Background: Childhood cancer survivors (CSS) are at risk for several late effects, among them increased risk of metabolic syndrome (MetS). We wanted to study if female hypogonadism was a risk factor for MetS.

Method: This study included 167 female CCS, mean age 34.3 (19.3-57.8) years in the South region of Sweden and 164 matched controls, mean age 35.0 (19.3-58.0). The female CCS were diagnosed at mean age 8.9 (0.1-17.9) years with a mean follow up time of 25.4 (11.6-41.3) years. The distribution of childhood cancer diagnoses was representative compared to the distribution of diagnoses in Sweden for females < 19 years. The odds ratio (OR) for MetS after different treatments and also ovarian insufficiency was studied.

Results: MetS was present in 14.4% (24/167) among CCS and in 2.4% (4/164) among controls ($p < 0.05$). OR for MetS in all CCS compared to controls was 6.7 (95% CI 2.3, 19.8). The highest OR was noted after treatment with cranial irradiation 9.3 (2.8, 31.1) or alkylating agents 9.1 (2.9, 28.4), but also for those with premature ovarian insufficiency (POI) 8.9 (2.0, 38.6) (hypothalamic-pituitary POI excluded).

Conclusion: The incidence of MetS was higher in females treated for childhood cancer compared to controls. In addition to established risk factors as cranial irradiation and chemotherapy the presence of POI also significantly increased the risk for developing MetS.

Presentation: poster

Thyroid

P1-420

The Genetic and Clinical Characteristic of Pediatric Patients with Congenital Hypothyroidism Gland In-Situ

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Introduction: The underlying genetic causes of congenital hypothyroidism with gland in-situ (CH GIS) and hyperthyrotropinemia (HT) remain largely a mystery. Thanks to NGS, genetic screening is now finding many novel variants. The challenge is to correctly identify which genes and which variants lead to CH and which cause only a transient HT.

Objectives: Our objectives were to evaluate the presence of variants in 14 candidate genes (*TG, DUOX2, DUOXA2, TPO, TSHR, PAX8, GLIS3, SLC5A5, SLC26A4, NKX2-1, NKX2-5, JAG1, IYD, FOXE1*) using NGS in patients diagnosed with CH GIS and clinically reevaluated later in life. We wanted to compare the clinical data of the patients with their genotype.

Materials and Methods: 56 pediatric patients who were initially diagnosed with CH GIS and began L-T4 replacement therapy all underwent a clinical reevaluation between 3-5 years of age and were diagnosed with either CH GIS, permanent HT, or transient HT. All 56 underwent NGS screening of 14 candidate genes.

Results: 45/56 patients (80.36%) had a variant in the candidate genes (16 had one variant, 18 had two, 11 had three or more). These variants were distributed over 73 distinct sites in 11 genes: *TG* had 21 distinct variants (17 novel), *DUOX2* had 21 (12 novel), *TPO* had 8 (7 novel), *TSHR* had 6 distinct (2 novel), *PAX8* 4 distinct (3 novel), *GLIS3* had 6 distinct (all novel), *SLC5A5* had 3 distinct (all novel), and *SLC26A4*, *NKX2-1*, *JAG1*, *IYD* each had 1 (all novel). *DUOXA2*, *FOXE1*, and *NKX2-5* were unaffected. 54/73 (74.0%) of these variants were novel and have never been reported in literature. Only 5/73 of the variants were homozygous, the rest were heterozygous. A spectrum ranging from transient HT to CH GIS was observed however, patients with variants in genes controlling gland formation (*GLIS3* and *PAX8*) had either a transient HT or CH GIS.

Conclusion: Although a genetic screening program for CH GIS patients is still a long way off, information from studies utilizing NGS is giving clinicians a clearer picture of the underlying causes. While the etiology is mostly still unclear, studies such as this one help identify possible pathologic variants and lead to a better understanding of CH GIS.

P1-421

Zinc transporter 8 (ZnT8) as a new autoantigen in thyroid tissue – preliminary data

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Zinc (Zn) is a crucial trace mineral that regulates the expression and activation of biological molecules such as transcription factors, enzymes, adapters, channels, and growth factors, along with their receptors. Bioinformatics analysis of the human genome discloses that Zn may bind ~ 10% of all of the proteins found in the human organism. This remarkable finding highlights the physiological significance of Zn in molecules involved in cellular processes and thereby its essential role in development, differentiation, immune responses, neurological functions, and protein synthesis.

We studied the expression of ZnT8 transporter in thyroid tissues from patients with immune and non-immune thyroid diseases. The study was performed in thyroid tissues after thyroidectomy from patients with thyroid nodular goiter (n=12, mean age 16.5 years ± 4) and cases with Graves' disease (n=13, mean age 14.6 years ± 2.5).

In our study we investigated the expression of ZnT8 in human thyroid tissues from patients with immune and non-immune thyroid diseases using immunohistochemistry, Western Blot as well as immunofluorescence analyses. To the best of our knowledge, this is the first investigation which identified ZnT8 protein expression in human thyroid tissues, moreover, confirmed by three different laboratory techniques.

1. Expression of ZnT8 transporter was identified by immunohistochemistry in the thyroid tissues from pediatric patients with Graves' disease (on +++) and nontoxic nodular goiter (on ++).
2. ZnT8 transporter expression was found both in thyroid follicular cells (within the cytoplasm and cytoplasmic membrane in follicular cells) and C cells (membrane-cytoplasmic reaction) in fluorescence.
3. Predominant expression of ZnT8 in band 41 kDa (cases: 2,3,5,7,10,14,15,16,17,19) in immune than in non-immune (cases: 1,4,6,8,9,18) thyroid disorders (Fig.1) may suggest potential role of ZnT8 as a new thyroid autoantigen but it requires further study on a larger cohort.

P1-422**Prospective Evaluation of Autoimmune and Non-Autoimmune Subclinical Hypothyroidism in A Large Cohort of Children and Adolescents with Down Syndrome**

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Objectives: Subclinical hypothyroidism (SH) is the most common thyroid abnormality in Down Syndrome (DS) children (25-60%); its etiology remains still not completely clarified. Aim of this prospective multicenter study was to evaluate prevalence and natural course of autoimmune and non-autoimmune SH in a large cohort of DS children and adolescents.

Methods: The study population included 101 DS patients with SH (TSH 5-10 mIU/L; FT4 12-22 pmol/L), aged 2-17 years at SH diagnosis. DS children with congenital hypothyroidism or early onset isolated hyperthyrotropinemia were excluded. Annual monitoring of TSH, FT4, BMI and height was performed for 5 years. Thyroglobulin autoantibodies (TGAbs) and thyroid-peroxidase autoantibodies (TPOAbs) were tested at diagnosis and at the end of follow-up.

Results: 37/101 (36.6%) patients displayed autoantibodies positivity (group A); the remaining 64 (63.4%) were classified as non-autoimmune SH (group B), ($p=0.0001$). Group A was characterized by higher median age at SH diagnosis and by more frequent family history of thyroid disease (6.6 vs 4.7 years, $p=0.001$; 32.4% vs 7.8%, $p=0.001$ respectively), whereas congenital heart defects were more common in group B (65.6% vs 43.2%, $p=0.028$). Gender, median BMI (SDS), height (SDS), FT4 and TSH were similar between the two groups. At the end of follow-up: 35.1% of group A patients developed an overt hypothyroidism (OH) vs 17.2% of group B ($p=0.041$); 31.25% of group A vs 10.8% of group B became biochemically euthyroid ($p=0.02$); 37.8% of group A vs 51.5% of group B maintained, over time, SH condition ($p=0.183$). Overt hyperthyroidism was only observed in group A (16.2%, $p=0.004$). Logistic regression suggested autoimmunity (OR=3.2) and baseline TSH values (OR=1.13) as predictive factors of evolution from SH to OH.

Conclusions: In DS children, non-autoimmune SH showed higher prevalence and earlier onset. The risk of thyroid function deterioration over time, from SH to OH, seems to be influenced by autoimmune etiology and higher baseline TSH values.

P1-423**Congenital hypothyroidism (CH) detected by the second newborn screening in Lombardia region: incidence and evolution of CH**

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Introduction: Although there are several studies on the incidence of congenital hypothyroidism (CH), there are few data showing incidence and evolution of CH detected by the second newborn screening (NBS).

Objectives: To assess the incidence of CH in Lombardia region and the percentage of patients identified by the 2ndNBS. To describe the clinical features and evolution of CH patients detected by the 2ndNBS.

Methods: The 1stNBS (cut-off blood-TSH \geq 10mU/L) was performed at 2-5 days in all neonates born in Lombardia region. The 2ndNBS (cut-off blood-TSH \geq 5mU/L) was performed in selected cases (prematurity, weight $<$ 2000g, malformations/syndromes, admission in NICU, twins, steroid treatment, maternal thyroid disease, borderline 1stNBS and associated risk factors).

Clinical data at diagnosis and re-evaluation of patients detected by the 2ndNBS (period 2007-2014) and followed-up at a single tertiary centre for paediatric endocrinology were collected. At 2-3 years, patients with gland in situ (GIS) underwent re-evaluation and were classified as permanent CH (s-TSH $>$ 10mU/L), persistent hyperthyrotropinemia (HT) (s-TSH 5-10mU/L), and transient CH (s-TSH $<$ 5mU/L).

Results: In the period 2007-2014, 767,157 newborns were screened for CH. 842 patients identified by NBS (67.6% by the 1stNBS, 32.4% by the 2ndNBS) were diagnosed with CH and treated with levothyroxine. The incidence of CH confirmed at birth (permanent and transient CH) was 1:911. Among the patients detected by the 2ndNBS, 101 were followed-up at our clinical centre: 38.6% were preterm, 15.8% had additional malformations. At diagnosis, s-TSH was between 10.31-756.60 mU/L (median: 34.25mU/L), mean s-FT4 was 0.87 ± 0.39 ng/dl. Thyroid ultrasound showed 5 babies with thyroid dysgenesis and 96 with GIS. At reevaluation, among the patients with GIS 14 showed permanent CH (14.6%), 29 persistent HT (30.2%), and 53 transient CH (55.2%). Genetic analysis performed in 23 patients with GIS showed genetic variants in genes associated with CH in 12 cases (DUOX2:9 cases, TSHR:2 cases, PAX8:1 case).

Conclusion: Between 2007 and 2014 the incidence of CH confirmed at birth in Lombardia region was 1:911. In the absence of the 2ndNBS the incidence would have been 1:1348. In our cohort, preterm infants were 38.6%, indicating that other risk factors can contribute to delayed TSH elevation. In addition, the frequency of malformations was higher than expected. Although the majority of patients identified by the 2ndNBS had transient CH and HT, the 2ndNBS allowed the identification of severe cases of CH, cases of thyroid dysgenesis, and cases of CH caused by genetic variants in genes associated with CH.

Transition for patients with chronic thyroid diseases

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Background: Children and adults with chronic thyroid disorders (TD) need continuous monitoring as periods of inadequate thyroid hormone substitution can impact metabolism, puberty and fertility. Transition from pediatric to adult-oriented care is often characterized by discontinuity in care resulting in poor health outcomes and impaired quality of life. Transition care (TC) for young adults with TD remains largely unknown.

Objectives: To analyze the TC of patients with chronic TD and to create a specific transition passport aiming to improve patient autonomy

Methods: In this pilot project, patients followed at our tertiary care center for a chronic TD (congenital hypothyroidism, thyroiditis, secondary hypothyroidism) were contacted after transition from pediatric to adult care and asked to answer 1) a structured transition questionnaire, 2) the 26 item WHOQOL-BREF questionnaire, and 3) the 3-item "Adherence Estimator" for medical prescription.

Results: 29 patients (69% females, mean age 23.2 years (17-34); 41% Hashimoto thyroiditis, 24% Graves disease, 21% congenital hypothyroidism, 14% other) responded. Quality of life was good or excellent in 89.8%. 27.6% did not feel well accompanied during transition. 51.7% felt that a transition involving the pediatrician and the adult specialist would be adequate, 17.2% would prefer to see the adult specialist alone. 27.6% felt that their treatment was not important. During the last month, 17.1% admitted to forget the medication 1-2 times and 17.1% more than 3 times.

Conclusion: Whilst quality of life was good, around 1/3 of the patients with TD did not feel satisfied with TC, and medication adherence seemed insufficient. Our results reflect the special attention required by young adults with chronic diseases. In order to improve TC, we developed a structured transition program including a novel interactive transition passport aiming to enhance autonomy and therapeutic adherence through education and guidance to patients and medical caregivers.

Maternally inherited resistance to thyroid hormones with discordant postnatal phenotypes in two infant brothers

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Resistance to thyroid hormone due to mutations inactivating thyroid hormone receptor-Beta occurs in one in 40,000 individuals and can arise de novo or be inherited, generally in a dominant fashion. Clinical manifestations are widely variable and include failure to thrive in infancy. The biochemical diagnosis is usually straightforward: high serum fT₄ and non-suppressed TSH.

We report two brothers who both inherited the known c.728G>A, p.R243Q mutation in TRHB from their mother, who had been diagnosed at age 20 in the course of blood work for fatigue: fT₄ 31 pmol/L, TSH 2.8 mU/L. Both pregnancies were uneventful, except for the ultrasound finding in sibling # 2 that the right kidney was small and contained multiple cysts. As there was no indication of fetal hyperthyroidism, no prenatal diagnosis was attempted. Both were born at 37 weeks, with birth weights of 2926g for sibling #1 and 2920g for sibling #2. Sib # 2 had a preauricular tag. Both sibs had inherited the maternal mutation. There was neither sign of thyroid dysfunction nor goiter. On day 2, blood spot TSH was 1.4 and 5.2 mU/L; serum TSH was 3.28 and 4.26; fT₄ 39.6 and 53.37, respectively. Both were discharged on day 2 and exclusively breastfed. However, sibling # 2 was admitted on day 5 for stridor. Laryngomalacia was diagnosed. On day 10, a CT angiogram was performed and did not show any malformation of the heart or vessels. At 2 months, the association of failure to thrive (weight - 3 SD) with laryngomalacia and abnormal right kidney development led to the diagnosis of Di George syndrome (22q.11 deletion). This deletion was absent in the parents. Feeding with an enriched formula led to catch-up growth.

To our knowledge, sibling # 2 is the first reported case of simultaneous RTH and 22q11 deletion. While there is no obvious biological link between the two conditions, it is the contrast with the postnatal evolution of sibling # 1 that led us to broaden the diagnostic investigations in sibling # 2.

P1-426

A rare case of familial heterozygous Thyroid hormone receptor beta (THR β) mutation presenting with dilated cardiomyopathy

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Background: Resistance to thyroid hormone beta (THR β) is a clinical spectrum which varies in presentation even between individuals with the same mutation. Life-threatening cardiac dysfunction is recognized in homozygous THR β state but never reported in cases of inherited heterozygous THR β defects.

Aim: We report the first case of familial inherited heterozygous (THR β) beta mutation presenting with severe dilated cardiomyopathy.

Case Report: Previously well, 9-month-old girl, presented with one-week history of lethargy, respiratory distress and resting tachycardia (HR 170-200bpm). Chest X-ray identified cardiomegaly. Echocardiogram confirmed heart failure with dilated cardiomyopathy. Clinical investigations revealed markedly abnormal thyroid function tests (TFT) with no goiter [TSH 4.81(0.5-3.8mU/L), fT4 50.6(10.8-22.9mU/L), fT3 17.2(3.6-6.8pmol/L)] and vitamin D insufficiency (37nmol/L). Parents were unrelated of Jamaican origin. Infant's father died aged 31years, from sudden cardiac arrest with underlying untreated hyperthyroidism and severe dilated cardiomyopathy of unknown etiology. Father had Thyroid Hormone Resistance (RTH) with (THR β) heterozygous mutation; c.928A>T, p.M310L. Genetic screening confirmed inheritance of the paternal THR β mutation in our patient and her older sister aged 3yrs [TSH 2.26(0.5-3.8mU/L), fT4 45(10.8-22.9pmol/L), fT3 12.4(3.6-6.8pmol/L)], whose echocardiogram is normal to date. Vitamin D insufficiency was treated but did not improve poor cardiac indices.

Over ensuing months, our patient had persistent cardiomyopathy with reduced cardiac function (ejection fraction (EF) 15-20%), required respiratory and inotropic support and was listed for urgent cardiac transplant. It was unclear if the tachycardia was secondary to cardiotoxic hyperthyroxinemia or directly secondary to cardiac failure. Carbimazole was commenced (0.9mg/kg/day) to reduce hyperthyroid additive strain on the heart, despite which fT3/fT4 remained significantly elevated. By week 6of Carbimazole, tachycardia and clinical status improved with elevation in TSH 17.36(0.5-3.8mU/L). To circumvent this, patient was treated with TRIAC (3,5,3'-triiodothyroacetic acid), a centrally acting thyroid hormone analog, effective in the management of childhood THR β . This was associated with simultaneous improvement in cardiac function (EF \geq 51%). The patient came off the transplant list after 5 months of inpatient care and was discharged home on oral feeds. Genetic cardiomyopathy screens in affected cases were negative.

Conclusion: This is the first case-report of an infant with heterozygous THR β mutation requiring combined Carbimazole and TRIAC treatment for concurrent life-threatening cardiac dysfunction. The critical status of our patient, in-conjunction with sudden death of her untreated father and potential risk of evolution of disease in her sister, demonstrates that heterozygous THR β is a clinical entity that requires ongoing active monitoring and management.

P1-427

Acquired Hypothyroidism in a Toddler: An Unusual Presentation of Langerhans Cell Histiocytosis

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Introduction: A 23-month-old male was admitted for evaluation of an enlarging neck mass, persistent rash, and periorbital edema.

Case Description: The toddler had a strikingly large neck mass which had rapidly progressed over 1 month. He presented with a pustular and petechial rash primarily on his scalp which had been unresponsive to multiple treatment modalities. Initial work-up for his neck mass revealed a TSH of 19.7mU/L (0.4-6.0mU/L). His TSH on the Newborn Metabolic Screen was normal. He consumed an iodine replete diet. Anti-thyroglobulin and anti-thyroid peroxidase antibodies were negative. Repeat TSH was 28.6 mU/L and free T4 was 6.8 pmol/L (8.0-20.0pmol/L). Thyroid ultrasound demonstrated a diffusely enlarged and hypervascular gland, indicating high metabolic activity which is atypical in a biochemically hypothyroid patient.

The initial biopsy of his skin lesions was suboptimal for evaluation and did not show any obvious inflammatory infiltrate. There was no suggestion of infiltrative disease based on liver enzymes and peripheral blood smear. Lymphopenia was identified and the working diagnosis shifted towards an immunodeficiency. Fine needle aspiration of the thyroid revealed atypical histiocytic infiltrate consistent with Langerhans Cell Histiocytosis (LCH). No normal thyroid elements were identified.

CT neck revealed a large soft tissue mass within the anterior neck exerting significant mass effect on the subglottic airway. The narrowest tracheal segment measured 6mm anterior to posterior.

Discussion: The patient was diagnosed with multisystem LCH. His acquired hypothyroidism was a result of LCH infiltration of the thyroid and compression of the normal thyroid glandular tissue. Toddlers rarely present with acquired primary hypothyroidism, and this case highlights the importance of considering infiltrative disease as an etiology in this age group. The patient required intensive care admission and was urgently treated with corticosteroids to manage the airway. It is crucial to consider and urgently manage external compression of the trachea and neck vessels when faced with a rapidly enlarging neck mass.

P1-428**Anti-gastric parietal cells antibodies for autoimmune gastritis screening: a follow-up study in young patients with autoimmune thyroid disease**

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Introduction: The association between ATD and AIG is very poorly characterized in pediatric age. We review the prevalence of the anti-gastric parietal cells antibodies (APCA) in young patients with ATD and we evaluated the development of AIG during follow-up, in order to define the usefulness of these markers for AIG screening in these patients.

Patients and Methods: We evaluated 220 children and adolescents (11.28 ± 6.37 yrs) with ATD (186 and autoimmune thyroiditis, AT and 34 Graves' disease, GD). At ATD diagnosis and annually thereafter, blood count and PCA levels were measured. In patients positive for PCA, plasma gastrin, cromogranin A, vitamin B12, iron and ferritin levels, H. Pylory antigen were detected. The PCA-positive patients >18 years were invited to perform gastroscopy.

Results: PCA positivity were detected in 10 (4.5%) subjects (5F/5M; 12.6 ± 3.4 yrs). The prevalence of PCA positivity was not significantly different in GD than in AT patients ($p=0.9$). PCA positivity was detected after 2.7 ± 2.7 yrs of follow-up in AT and 4.4 ± 4.0 yrs in GD ($p=0.4$). The autoantibodies positive patients were higher in males than females, both in AT and GD ($p=0.02$ and $p=0.03$, respectively). At the diagnosis of PCA positivity, five out of 10 PCA-positive patients had iron deficiency, 4 vitamin B12 deficiency, 2 anemia, 3 hypergastrinemia and 2 elevated chromogranin values. Two patient, shower H. pylori infection. Gastroscopy was performed in the 5 ATD and in all patients AIG was confirmed.

Conclusion: ATD and AIG may be associated also in juvenile population. PCAs is a usefull marker to detect the subjects at risk for this condition. Due to the longer life expectancy of the pediatric population and considering the relatively high risk of malignant transformation, an early surveillance monitoring is mandatory for children and adolescents with ATD.

P1-429**Genetic evaluation of congenital hypothyroidism with gland-in-situ using targeted exome sequencing**

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Objective: To analyze the genetic cause of congenital hypothyroidism by targeted exome sequencing in pediatric patients with congenital hypothyroidism with thyroid gland *in situ*.

Patient and Method: The study population comprised 20 patients with thyroid gland, who were diagnosed with congenital hypothyroidism at Pediatric Endocrinologic Clinic of Pusan National University Hospital. Targeted exome sequencing was performed on 8 causative genes, including the *TSHR* gene that may be present in the normal thyroid gland and *TG*, *TPO*, *DUOX2*, *DUOXA2*, *IYD*, *SLC26A4*, and *SLC5A5* genes that are known to cause thyroid dyshormonogenesis.

Results: Of 20 patients, permanent hypothyroidism, subclinical hypothyroidism, and transient hypothyroidism was found in 15 (75%), 3 (15%), and 2 (10%) patients, respectively. Targeted exome sequencing on 8 genes identified 24 variants among 16 patients: *DUOX2* – 11 variants in 8 patients; *TSHR* – 6 variants in 5 patients; *TG* – 5 variants in 3 patients; and *DUOXA2* – 2 variants in 2 patients. Among these 24 variants, 10 were novel variants. No variants were identified in *TPO*, *IYD*, *SLC5A5*, and *SLC26A4* genes. Two patients showed triallelic (digenic) mutations (*TG* and *TSHR* in one patient and *DUOX2* and *TSHR* in the other). No variants were identified in 3 patients with permanent hypothyroidism and 1 patient with transient hypothyroidism. Considering inheritance, genetic causes that could explain the phenotypes of congenital hypothyroidism were identified in 11 cases (55%).

Conclusion: Based on the findings, the genetic causes of congenital hypothyroidism by targeted exome sequencing in patients with thyroid gland *in situ* were identified in 55% of the cases, with *DUOX2* and *TSHR* gene mutation being the most common causes. As there were many novel variants, and the frequency of cases where the genetic mutations were unidentified was high (45%), additional studies on genetic causes of congenital hypothyroidism is warranted.

P1-430**Clinical Characteristics and Long-term Follow-up of Patients with Congenital Hypothyroidism (CH) due to Thyroid Peroxidase (TPO) gene Mutations**

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Background: Hereditary inborn errors of thyroid hormone synthesis account for 10-15% of congenital hypothyroidism (CH). Thyroid peroxidase (TPO) deficiency is the most common enzymatic defect with a frequency of 50-90%.

Aim: In the present study our objective was to characterize the long-term clinical outcome in patients with TPO deficiency and to assess the association between development of multinodular goiter (MNG) and the adherence to therapy.

Methods: Clinical and genetic data were collected retrospectively from birth up to 44 years. Data was acquired from the medical files of patients with TPO deficiency, followed at the Endocrine clinic at Ha'Emek Medical Center.

Results: 33 patients from 7 core families of Arab-Muslim descent were enrolled. All patients had CH due to TPO deficiency. The main symptoms at presentation were neonatal jaundice (36%), macroglossia (27%) and umbilical hernia (27%). At 1 year follow up 9 patients (27%) showed a delay in developmental milestones, although the majority had normal cognitive achievements at the time of the study. Three different mutations were identified in the *TPO* gene: 19 patients were homozygous to c.1618C, p. Arg540stop; 4 were homozygous to c.1478G>A, p.Gly493Ser; 4 were compound heterozygous to both mutations and 2 were homozygous to c.875C, p.Ser292Phe. At diagnosis, 4 patients presented with goiter; however over time, 22 patients developed MNG (61%), at an average of 8.6 years. Eight patients underwent thyroideectomy, one was diagnosed with follicular thyroid carcinoma and the other seven had either follicular hyperplasia or adenoma. When comparing TSH levels between patients who developed goiter to those who did not, no correlation was found between lifetime non-adherence (TSH levels >5mIU/L) and goiter development or the need for thyroideectomy.

Conclusion: This cohort is the largest, long-term follow up of patients with *TPO* mutations and their clinical manifestation. Our results indicate that elevated TSH alone cannot explain the high rate of goiter development in patients with *TPO* mutations, suggesting that TPO itself may have a role in thyroid growth suppression. The high rate of MNG development with time and the risk for thyroid carcinoma indicates the need for long-term follow-up in these patients.

P1-431**The relationship between perfluoroalkyl compounds concentrations at ages 2, 4, and 6 years and thyroid function in early childhood: a prospective cohort study**

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Background: Perfluoroalkyl compounds (PFCs) have been suggested as potential thyroid disrupting chemicals. However, previous studies about the associations between PFCs and childhood thyroid function are scarce, and inconclusive. We evaluated the PFC exposure in Korean preschool children, and investigated the temporal relationship with thyroid hormone concentration.

Methods: From a prospective Environment and Development of Children (EDC) cohort study, we used data on 14 kinds of PFCs concentrations at ages 2, 4, and 6 years and thyroid function test (Serum thyroid stimulating hormone [TSH] concentrations at ages 2, 4, and 6 years, and free thyroxine [FT4] and triiodothyronine [T3] and TSH concentrations at 6 years of age).

Results: When young children were serially followed-up from ages 2, 4, to 6 years, perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA) were detected in >90% of the serum samples. After adjusting for age, body mass index and iodine intake, the association between serum PFC concentrations and thyroid function were significant among boys, but not among girls. For TSH levels, both PFDA and PFOS concentrations at 2 years of age were inversely associated with TSH levels at 2 years of age ($P<0.05$ for both), and serum PFNA concentrations at 6 years of age was negatively related to TSH levels at 6 years of age ($P=0.044$). Serum FT4 levels at 6 years of age was positively associated with PFNA concentrations at 2 years of age ($P=0.009$) and PFOA concentrations at 6 years of age ($P=0.018$). In addition, serum T3 levels at 6 years of age were positively associated with PFNA concentrations at ages 2 and 4 years, and PFOS concentrations at 6 years of age ($P<0.05$ for all).

Conclusion: PFOS, PFOA, PFHxS, PFDA, and PFNA were consistently detected >90% in Korean children from ages 2, 4, to 6 years. Significant effect of PFCs on increased FT4 and T3 and decreased TSH levels was found among boys.

Levothyroxine Effect on Thyroid Volume in Children with Autoimmune Hashimoto Thyroiditis (AHT) Presenting Subclinical (SH) or Overt (OH) Hypothyroidism

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Objectives: Assess thyroid volume in relation to TSH and FT4 at diagnosis of AHT and 2.9 years of follow up in children with SH or OH.

Methods: Two hundred one children (155 girls) with AHT were divided according to TSH and FT4 levels [SH-FT4 > 1.0 ng/dl: Group 1: TSH: 5-7.5 mU/l, Group 2: TSH: >7.5 mU/l, OH: Group 3: TSH > 7.5 mU/l and FT4 ≤ 1.0 ng/dl]. Mean L-T4 dose is reported in µg/Kg/day. Thyroid volume was calculated by the modified formula of the rotation ellipsoid: Vol (mL)= 0.479 (depth x width x length). TV was defined as the sum of the volumes of both lobes (isthmus not included).

Results: Main characteristics are shown in table 1. At diagnosis, TSH, FT4 levels, L-T4 dose and thyroid volume were significantly different ($p<0.05$) between SH (groups 1 and 2) as compared to OH (group 3). At follow-up all patients were euthyroid and TSH and FT4 levels did not differ significantly between groups. L-T4 dose was significantly higher in OH as compared to group 1 but not group 2. Thyroid volume did not differ significantly among groups.

Table 1. Data are shown as means (SD).

	Group 1 (n=70)	Group 2 (n=72)	Group 3 (n=59)	*p
AT DIAGNOSIS				
Age (yrs)	10.4 (2.6)	8.9 (2.6)	9.6 (2.4)	
Height z-score	0.55 (0.9)	0.52 (1.0)	0.43 (0.9)	
BMI z-score	0.87 (0.9)	0.93 (0.9)	0.92 (1.1)	
TSH (mU/l)	6.1 (0.7)	10.9 (5.6)	47.9 (74.2)	*
FT4 (ng/dl)	1.2 (0.2)	1.3 (0.16)	0.85 (0.1)	*
L-T4 (µg/Kg/day)	1.1 (0.39)	1.3 (0.51)	1.5 (0.6)	*
Thyroid volume (ml)	8.0 (4.3)	6.3 (3.7)	10.1 (6.3)	*
AT FOLLOW UP (yrs)				
Age (yrs)	13.2 (2.4)	12.1 (2.7)	12.6 (2.4)	
Height z-score	0.56 (1.0)	0.59 (0.9)	0.43 (0.8)	
BMI z-score	0.82 (0.8)	0.76 (0.9)	0.92 (0.9)	
TSH (mU/l)	2.2 (1.2)	2.6 (1.2)	2.2 (1.1)	
FT4 (ng/dl)	1.4 (0.2)	1.4 (0.4)	1.3 (0.2)	
L-T4 (µg/Kg/day)	1.1 (0.3)	1.4 (0.4)	1.6 (0.7)	*
Thyroid volume (ml)	7.7 (4.1)	6.7 (3.9)	8.4 (3.5)	

*One-Way Analysis of variance (ANOVA), $p<0.05$.

Conclusion: At diagnosis, L-T4 needs and thyroid volume are significantly lower in SH patients as opposed to OH patients. At 2.9 yrs, children with OH receive significantly higher LT-4 doses than those with SH and TSH < 7.5 mU/l but similar with those of SH and TSH > 7.5 mU/l and all present similar thyroid volumes.

Late Breaking Posters

LB-1

A trial investigating the long-term efficacy and safety of two doses of Norditropin® (somatropin; recombinant human growth hormone) in Japanese children with short stature due to Noonan syndrome over four years of treatment

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Objectives: This trial (NCT01927861) evaluated the growth-promoting effect and safety of Norditropin® (somatropin; recombinant human growth hormone) in Japanese children with short stature due to Noonan syndrome over four years of treatment.

Methods: Pre-pubertal children diagnosed with Noonan syndrome were randomized 1:1 to receive Norditropin® 0.033 mg/kg/day or 0.066 mg/kg/day. Change in height standard deviation score (SDS) from baseline to 208 weeks (four years) of treatment was analyzed using an ANCOVA model.

Results: Fifty-one children were randomized to Norditropin® 0.033 mg/kg/day (n=25, mean age [mean±SD] 6.57±2.42 years, 11 female) or 0.066 mg/kg/day (n=26, mean age 6.06±2.25 years, 8 female). Baseline height SDS was similar between groups, relative to a Japanese reference standard (0.033 mg/kg/day: -3.24±0.76; 0.066 mg/kg/day: -3.25±0.71) or a Japanese Noonan reference standard (0.033 mg/kg/day: -0.73±0.74; 0.066 mg/kg/day: -0.80±0.72). After 208 weeks of treatment, the estimated change (95% CI) in height SDS relative to the Japanese reference standard was 0.85 (0.59; 1.12) in the 0.033 mg/kg/day group and 1.84 (1.58; 2.10) in the 0.066 mg/kg/day group, with an estimated mean difference of 0.99 (95% CI: 0.62; 1.36) ($p<0.0001$). Rates and patterns of adverse events (AEs) and the frequency of serious AEs were similar between groups. Mean insulin-like growth factor-I SDS increased from -1.71 at baseline to -0.75 (0.033 mg/kg/day) and to 0.57 (0.066 mg/kg/day). HbA_{1c} increased slightly in both groups. Glucose profiles were almost unchanged and insulin profiles increased in both groups using an oral glucose tolerance test. Three patients in the 0.066 mg/kg/day group withdrew from the trial, two due to adverse events (polymyositis and scoliosis).

Conclusions: Japanese children with short stature due to Noonan syndrome treated with Norditropin® 0.033 or 0.066 mg/kg/day over 208 weeks showed significantly improved height SDS

and a favorable safety profile. The increase in height SDS was statistically significant in the 0.066 mg/kg/day group compared with the 0.033 mg/kg/day group.

LB-2

The effects of different diets (high fat and high fructose diet) on the development of insulin resistance and tissue advanced glycation end product levels in rats

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Introduction & Objectives: Fat and fructose-rich nutrition bring many metabolic diseases, especially obesity and diabetes. Recent years, more scientific interest in how can diet effect on brain function has emerged. We aimed to investigate the effect of high fructose and high-fat diet on the brain, and whether the presence of relationship with advanced glycation end products histologically, in rat model.

Materials & Methods: Twenty-four Sprague Dawley rats were used and divided into 3 groups as control group, high fructose group and high fatty group. During 12 weeks, while the rats in the control group were given standard rat chow, those of in the high fructose and high fatty group were fed with %60 high fructose diet and %45 high fat diet, respectively. At the end of the experiment, their brains were removed. AGE and R-AGE expression were evaluated by immunohistochemistry and biochemically.

Results: In the H-E stained sections, the control group rat brains showed healthy histological appearance. The brain sections of the high fructose group showed that histological structure was deteriorated. There was a significant increase in glial cells, especially in the mediobasal hypothalamus. Shrinkage and eosinophilic staining of the neurons were noticed, chromatin condensation in the nucleus was prominent. Also, pericellular edema was present in neurons and glial cells. Similar findings were observed in the high-fat group. Glial cells were increased compared to the control group but were less than the high fructose group. There was dilated blood vessels and pericellular edema. Small eosinophilic neurons with shrunken nuclei and with condensed chromatin were also abundantly observed in the high-fat group. In the control group, no AGE immunostaining was observed in the axonal structures, whereas immunopositive staining was observed in neural cells. When the brain sections of high fructose group were examined, it was observed that AGE immunostaining positivity was more significant than the control and high-fat group. R-AGE immunostaining intensity in hypothalamus of both high fructose and high-fat groups was higher than in the control group. Biochemical results are given in Table 1.

Conclusions: The feeding with both high fructose and high-fat diet might cause the deterioration in the brain mainly the hypothalamus, and increased advanced glycation end products may play an essential role in the development of damage.

	Control Brain	High fructose Brain	High fat Brain
Glucose µmol/L	25,86	25,09	19,42
Insulin ng/mL	17,93	16,25	17,09
R-AGE pg/mL	93,24	169,42	163,78
GEs ng/mL	132,73	86,85	100,36

LB-3

Insights into the regulation of androgen biosynthesis from males with congenital hypogonadotropic hypogonadism: quantification of bioactive steroid hormones reveals differences between gonadotropin replacement and testosterone replacement

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Background: In males with congenital hypogonadotropic hypogonadism (CHH), LH/FSH stimulation of gonads is deficient. In clinical practice, two hormone replacement strategies are employed to induce and maintain virilisation: Treatment with testosterone and gonadotropin replacement with hCG/rFSH.

Objective: To delineate the role of gonadotropins in pathways of male androgen biosynthesis and to thereby better define the gonadal and adrenal contribution to the circulating steroid hormone pool.

Patients and methods: In 25 males with CHH, serum steroid hormone profiles (specifically precursors of testosterone and its metabolites) were analyzed, using liquid chromatography-tandem mass spectrometry (LC-MS/MS), once, while patients were undergoing hCG/rFSH treatment and again, while on testosterone replacement. Data were compared to those of healthy controls (matched for age, BMI and serum testosterone).

Results: On replacement with testosterone, decreased levels of progesterone, 17-hydroxy-progesterone (17-OHP) ($\Delta 4$ classic pathway of androgen biosynthesis) and androstenediol (alternative pathway of testosterone synthesis), and mildly decreased levels of androstenedione and were observed, as compared to controls. The backdoor steroid pathway for DHT synthesis, represented by androstanediol, was increased. Serum levels of DHEAS, DHT, E2 and 11-oxygenated C19 androgens (11-keto-A4 11-keto-T, 11-ke-to-DHT) were comparable to those of controls.

On hCG/rFSH replacement, classic $\Delta 4$ pathway hormones were normal, including 17-OHP, androstenedione, DHT, and progesterone (near-normal), as well as the $\Delta 5$ hormone DHEAS, the alternative T pathway steroid androstenediol and all above-mentioned 11-oxygenated C19 androgens. Androstanediol (backdoor DHT pathway) and E2 were increased.

Conclusions: In males with CHH, a replacement with hCG/rFSH mimics physiologic steroid hormone profiles better than a substitution with testosterone. Gonadotropins induce $\Delta 4$ classic pathway steroid production via 17-OHP and androstenedione and co-activate the alternative pathway of T biosynthesis via androstenediol. The backdoor pathway of DHT and synthesis of 11-oxygenated C19 steroids and DHEAS are activated independently of gonadotropins. The documented differences in steroid profiles may cause differential steroid hormone-mediated gene expression patterns in target tissues and may thus have consequences for long term male health.

LB-4

Resistance to thyroid hormone alpha associated with early-onset severe NASH

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Introduction: Resistance to thyroid hormone alpha (RTH α) is characterised by tissue-specific hypothyroidism associated with barely normal thyroid function tests. Clinical features include dysmorphic facies, skeletal dysplasia, growth retardation, constipation, dyspraxia and intellectual deficit. Hormonal assessment often shows decreased/low-normal free thyroxine (fT4) and increased/high-normal free triiodothyronine (fT3) concentrations, resulting in a low fT4/fT3 ratio, with a non-adapted normal thyroid stimulating hormone (TSH) level.

We describe the case of a 14-year-old *THRA* mutant girl who was diagnosed at birth with peripheric congenital hypothyroidism and who developed marked hypercholesterolemia and severe non-alcoholic steatohepatitis (NASH). Phenotypical presentation includes marked abdominal obesity, macrocephaly, macroglossia, short and large nose, micrognathia and low-implanted ears, associated with mild intellectual impairment.

Materials and methods: A panel of genes involved in congenital hypothyroidism was explored by next generation sequencing (NGS) on DNA sample. Pathogenic variant was confirmed by Sanger sequencing of exon 10 of the *THRA* gene for the proband and her mother.

Functional analysis was performed on HepG2 cell line using plasmid transfection of wild type (WT) TR α 1 and TR β , mutated TR α 1 and reporter plasmids containing thyroid hormone responsive elements coupled to the luciferase gene. Transcriptional effect has been assessed through luciferase activity.

Results: Next generation sequencing identified a heterozygous single nucleotide c.1207G>A (p.E403K) *THRA* mutation on exon 10 resulting in impaired function of $\alpha 1$ receptor isoform. The patient's mother carried the same *THRA* mutation.

Transfection studies on HepG2 cells showed a significant lower transactivation effect of the mutant TR α 1 compared to WT TR α and a dominant negative transcriptional effect of mutated TR α 1 on both WT TR β and TR α .

Discussion: This peculiar case associates classical clinical and biological features of RTH α with a previously unreported first-plan metabolic profile: obesity, hyperlipidaemia and severe NASH. Functional in vitro studies suggest a dominant negative effect of mutated TR α 1 receptor on wild type TR β , which is the main isoform expressed in the liver, as well as on wild type TR α , which is mainly represented in adipose tissue. Taken together, these data suggest a pathogenic role of TR α 1^{E403K} in the development of this unique hepato-metabolic profile.

This case further strengthens the wide phenotypical variability of RTH α presentation and the pleiotropic effect of TRs.

non-ADHD control). We calculated ADHD heights SDS using the control sample statistics (gender and age specific) and analyzed individual's height SDS difference before and after treatment by t-test.

Results: there were 7172 ADHD and 16240 non-ADHD controls. The height curves were nearly overlapping. There was neither difference between gender specific median height curve of ADHD before treatment, non-ADHD control and ADHD after treatment (in both genders). Analysis of the individual's height SDS differences based on the control sample statistics revealed mean height SDS for HDHD males before treatment of 0.027 and height SDS of -0.046 after treatment, and mean height SDS for HDHD females before treatment of 0.086 and height SDS of 0.030 after treatment.

Discussion and conclusions: The study results support evidence that neither ADHD nor ADHD stimulants treatment nor their combined effect have significant effect on linear growth.

LB-5

Height curves and Height SDS in ADHD children measured before and after stimulant treatment are not affected - observation study in 7172 ADHD children

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Background: Attention deficit hyperactivity disorder (ADHD) is a common pediatric disorder with ongoing debate in the literature about its association with growth impairment. Most studies have focused on stimulants treatment effect while others suggested direct effect of ADHD. The present study compared height growth of ADHD children each measured before and after stimulant treatment.

Methods: We conducted historical prospective study based on Israeli largest health services provider (Clalit Health Services, 55% of the total population) database. Inclusion criteria were ADHD children 5-18 years old before treatment that eventually received stimulant medications consumed at least for 2 months and accordingly had documented anthropometrics before and after stimulant treatment. A non-ADHD control group derived from the general population of the same birth cohort ages 5-18 was also retrieved as the basis for local Standard Deviation Score (SDS) calculations. Exclusion criteria were documented co-morbidities in either group. We compared gender specific median height curve of the three groups (ADHD before and after treatment and

LB-6

Can different diets (high fat and high fructose diet) affect insulin resistance, tissue advanced glycation end product levels in rats' pancreas

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Introduction & Objectives: High consumption of processed foods rich in fat and sugar are associated with the increasing prevalence of metabolic disturbances like obesity, insulin resistance, dyslipidemia, type 2 diabetes mellitus. In the present study, we aimed to investigate the relationship between advanced glycation end products and metabolic disorders such as insulin resistance caused by high fructose and high-fat diet, and also examine histological changes in the pancreas, in a rat model.

Materials & Methods: Twenty-four Sprague Dawley rats were randomly divided into three groups (8 rats per group) as control, high fructose and high-fat groups. The rats of control group were given with normal rat control diet. In the high fructose group; the rats were fed with %60 high fructose diet and in the high fatty group, the rats were given %45 high fat diet. After 12 weeks, rats in all groups were euthanized under anesthesia. Blood samples for biochemical analysis and tissue samples for histological investigation were taken. Tissue sections were stained with immunohistochemical staining for detection of AGE and R-AGE expression.

Results: Biochemical results were given in Table. In the pancreas of rats fed with high fructose diet and high-fat diet, the normal histological structure was observed to be impaired both in the exocrine and endocrine sections.

Rats fed with high fructose feed had intracellular swelling and vacuolization in islet cells and edema was seen in intercellular areas. In rats fed with fatty diet, interstitial edema, swelling of cells and intracytoplasmic vacuoles were observed in the Langerhans islets and the nuclei of some cells were lost. AGE and R-AGE immunopositivity both in the high fructose and high-fat groups were increased when compared with the control group.

Conclusion: Our results showed that high fructose and high-fat diet lead to both exocrine and endocrine pancreas injury, and this damage may be related to high expression of AGE and R-AGE.

Table: Biochemical results

	Control group Pancreas	High fructose group Pancreas	High fat group Pancreas
Glucos µmol/L	7,46	11,56	20,26
Insulin ng/mL	38,68	29,30	43,29
R-AGE pg/mL	467,23	203,02	459,38
AGEs ng/mL	39,50	40,20	78,90

LB-7

Long-Term Evaluation of Ovarian Function and Follicular Reserve in Patients with Malignant Diseases Treated with Chemotherapy in Prepubertal or Pubertal Age

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The survival rate of young patients with cancer has greatly improved in the last decades, in part due to the introduction of new therapeutic agents and protocols.

Chemotherapy may be associated with risk of ovarian dysfunction, permanent or transient amenorrhea, symptoms of ovarian insufficiency and infertility.

It has been suggested that prepubertal ovary is less susceptible to deleterious effect of chemotherapy.

Pre-clinical studies suggested that hormonal suppression of the hypothalamic-pituitary-ovarian axis could minimize the impact of cytotoxic agents on the ovary. The effectiveness of gonadotropin-releasing hormone agonists (GnRHAs) in preventing the impairment of ovarian function due to exposure to cytotoxic agents in pubertal girl is still controversial.

AMH is expressed by the ovarian granulosa cells of primary, preantral and small follicles. It is independent of gonadotropins, representing an ideal surrogate for ovarian reserve.

Objective: To evaluate long-term ovarian function in female adolescents with history of malignant diseases treated with chemotherapy at prepubertal or pubertal stage.

Material and methods: Female adolescent patients with history of malignancy who required chemotherapy were analyzed at least two years after menarche. A transversal study was conducted to evaluate gonadal function measuring gonadotropins (ECLIA) and AMH (ELISA) levels after at least two-year treatment withdrawal.

Patients were divided into two groups, group A: patients treated at pubertal stage who received chemotherapy concomitant with GnRHAs; group B: patients treated at prepubertal stage only with chemotherapy.

Results: Thirty-nine patients were enrolled.

Median and range.

Serum LH and FSH were within normal levels in both group except in one patient from group A, who had hypergonadotropic hypogonadism. AMH levels were significantly lower in group A. Two patients from group A achieved fertility.

Conclusion: In this long term follow up study prepubertal girls who received chemotherapy and pubertal girls who received chemotherapy concomitantly with GnRHAs showed low rates of ovarian dysfunction. However, the decline of AMH levels in patients who received chemotherapy in pubertal stage could indicate a decreased follicular reserve, although the effect of age cannot be ruled out.

	Group A (n=21)	Group B (n=18)	P value
Chronological age at diagnosis (years)	14.3 (9.2-18.1)	6 (0.5-10.5)	<0.001
Age of evaluation (years)	17.5 (17-30)	17 (13.6-22.9)	ns
Menarcheal age (years)	12.4 (10-15)	12.0 (10.2-14.7)	ns
Regular menses (n)	20/21	18/18	ns
Hot flushes (n)	1/21	0/18	ns
LH mUI/ml	5.7 (1.23-65.7)	6.4 (6.8-14.8)	ns
FSH mUI/ml	6.5 (0.11-200)	5.7 (3.6-9.4)	ns
AMH (pmol/L)	16.2 (1.2-57.6)	26.0 (9.1-76)	0.02

LB-8**Detection of Cardiomyopathy in Egyptian Children and Adolescents with longstanding Obesity using cardiac marker NT-pro PNB and Speckled Tracking Echocardiography**

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Introduction: Obesity is considered a major risk factor for developing cardiovascular morbidity and mortality. Obesity affects the structure and function of the heart mainly by causing increased blood volume, elevated cardiac output, left ventricular (LV) hypertrophy, and LV diastolic dysfunction. All of which can play a role in causing heart failure.

Objective: This cross-sectional study aimed to evaluate the effect of longstanding obesity on cardiac functions resulting in cardiomyopathy, to correlate the level of plasma NT-pro BNP biomarker to echocardiographic findings and to compare these values to apparently healthy normal controls.

Subjects and methods: A total of 80 obese children and adolescents above 8 years old with long standing obesity were included in the study. Patients with original cardiac disease or concomitant illness affecting the heart, those on medications known to affect cardiac functions and/or cases with syndromic obesity were excluded from the study. Study group were subjected to full history taking including age, sex, birth weight, onset of obesity, dietary habits, exercise habits, cardiac manifestations (palpitation, chest pain, dyspnea, easy fatigability, etc), family history of diabetes, hypertension or cardiac diseases. Thorough physical examination was done including anthropometry, blood pressure (BP) assessment as well as detailed cardiac examination. Biochemical evaluation included fasting lipid profile, HbA1c as well as the cardiac biomarker NT-pro BNP. Echocardiographic evaluation of the study group included conventional echodoppler measures, tissue velocity imaging (TVI) measure and 3D speckle tracking echocardiography (STE). Study population were compared to 40 non-obese healthy age and sex matched controls regarding NT-pro BNP level, tissue velocity imaging and speckled tracking echocardiography findings.

Results: The study showed statistically significant difference between cases and controls regarding plasma NT-Pro BNP and echocardiographic findings (tricuspid annular E'/A', left ventricular e/e', left ventricular GLS) ($p < 0.001$). Regarding echocardiography, 90% had LV systolic dysfunction, 67% had RV diastolic dysfunction and 100% had LV diastolic dysfunction within the study group. A statistically significant positive correlation was found between plasma levels of NT-proBNP and ventricular dysfunction (GLS) ($p = < 0.001$, $r = 0.888$). ROC curve showed that plasma NT-pro BNP level had a sensitivity of 84.7% and specificity of 87.5% in the diagnosis of cardiomyopathy using GLS as an echocardiographic parameter.

Conclusion: Longstanding obesity was associated with cardiomyopathy as evidenced by elevated levels of NT-proBNP and speckle tracking echocardiography (impaired ventricular systolic and diastolic functions). NT-pro BNP levels correlated significantly with LV systolic dysfunction.

LB-9**Left ventricular mass index and cardiovascular function in adolescents born small for gestational age (SGA)**

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Background: Subjects born small for gestational age (SGA) were shown to be at higher risk for metabolic consequences in adulthood but less is known on their cardiovascular function.

Objective and hypotheses: We aimed to investigate cardiovascular function and left ventricular mass index (LVMI) in adolescents born SGA and appropriate for gestational age (AGA) and their relationship with perinatal and postnatal factors.

Method: A prospective cohort of 47 SGA and 55 AGA children was followed-up from birth to adolescence (47 boys, 55 girls). At the time of the study, subjects were 11–14 years old (mean 12.5 ± 0.1 years). 7 (14.9%) of SGA children were short (height below 3rd percentile according to Lithuanian growth standards).

All participants underwent anthropometric measurements. Systolic and diastolic blood pressure (BP) were measured twice after 30min rest using an automatic device. Blood cholesterol analysis was performed after overnight fast. Echocardiography was performed in two-dimensional-guided M-mode. Left ventricular mass was calculated using the Devereux equation. LVMI was obtained using formula: $LVMI = LVM / \text{height(cm)}^{2.7}$.

Statistical analyses were adjusted for sex, age, pubertal stage and BMI_{SDS} . BP analysis was additionally adjusted for current height and LVMI – for systolic BP.

Results: SGA children without catch-up growth (SGACU-) had higher systolic and diastolic BP than those with catch-up growth (SGACU+) and AGA (Systolic BP: 125.1 ± 5.4 vs 111.2 ± 1.9 mmHg, $p = 0.015$ and vs 109.0 ± 1.7 mmHg, $p = 0.009$; diastolic BP: 76.9 ± 3.7 vs 66.5 ± 1.3 mmHg, $p = 0.006$ and vs 66.0 ± 1.1 mmHg, $p = 0.006$, respectively). LVMI was higher in SGACU- adolescents compared with AGA (31.3 ± 1.7 vs 27.5 ± 0.5 g/m^{2.7}, $p = 0.044$) but there was no difference in SGACU- vs SGACU+ adolescents. There was no difference in heart rate and cholesterol levels between SGACU-, SGACU+ and AGA groups.

LVMI in adolescence was directly related to current weight_{SDS}, BMI_{SDS}, waist-to-height ratio, systolic BP, glycaemia 120-min post-load, ALT and cortisol levels (all p<0.05). Moreover, LVMI was inversely related to increase in BMI_{SDS} and limb skinfold thickness from 6 to 12 years of age (all p<0.005) but directly related to increase in BMI_{SDS} from birth to 2 years of age ($r=0.328$, p=0.023) and the last one was the only factor independently related to LVMI in multiple regression model.

Conclusion: SGA adolescents without catch-up growth had higher systolic and diastolic blood pressure and LVMI compared with those with catch-up growth and AGA. BMI_{SDS} gain from birth to 2 years of age was an independent predictor of LVMI in adolescence.

LB-10

Irisin as a Mediator between Obesity and Vascular Inflammation in Chinese Children and Adolescents

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Objectives: The aim was to clarify the associations of Irisin with obesity and early onset metabolic and vascular sequelae in Chinese children, and to examine whether the association between obesity and endothelial dysfunction and vascular inflammation was mediated by Irisin.

Methods: We quantified Irisin serum levels in 85 lean and 120 obese children and assessed associations with metabolic and cardiovascular parameters in obese children. In addition, a potential direct effect of Irisin on endothelial activation was assessed in children.

Results: Irisin serum levels were significantly lower in obese children compared to lean children and correlated with physical parameters such as SDS-BMI, WC, VAI and ABSI. Moreover, we identified significant inversely associations with the measures of inflammation and markers of endothelial activation in obese children. Multiple regression analyses confirmed Irisin as the strongest predictor of SDS-SBP, Ang-2, ICAM-1, E-selectin and hsCRP independent of SDS-BMI. Lifestyle intervention results in a significant improvement of these cardiovascular and inflammatory parameters, and these were accompanied by significant improvement in Irisin and weight loss. Finally, in the mediation effect model, our data showed that Irisin changes act as partial mediators of the relationship between SDS-BMI changes and changes in inflammatory and endothelial parameters for ICAM-1, E-selectin and hsCRP after controlling for covariates.

Conclusions: We speculated that Irisin may have some influence on the early stages of cardiovascular disease in obese children.

LB-11

Height in Inborn Errors of Metabolism requiring hypoprotidic diet: a longitudinal follow up study about 213 patients

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Background: Protein intake is crucial for growth. Many inherited metabolic diseases (IMD) require a strict controlled protein diet.

Aim: To evaluate growth, pubertal status and body composition in IMD requiring a strict controlled protein diet.

Patients & Méthods: Longitudinal follow up cohort study. We recorded data before 4years (early childhood, n=189); between 4 and 8years for girls and 9years for boys (puberty, n=168) and after 8/9years (puberty, n=136).

Results: 213 patients (mean age: 13.9years) were treated for urea cycle disorders (n=77), organic acidurias (n=89), maple syrup disease (n=34), tyrosinemia type I (n=13). 69 patients attained their final height that was lower than their target height (SD_s): -0.90 (1.43) vs. -0.09 (0.85), p=0.0001. Mean height (SD_s) was lower than target height in each subgroup of age (p<0.0001). In the pubertal subgroup, height was lower compared to early infancy and to prepubertal subgroups (-0.9 (1.5) vs. -0.3 (1.3) and vs. -0.3 (1.5) respectively, p<0.0001). Tanner stage was assessed in 91(81%) patients. Delayed puberty was frequent (24/91, 25.3%). In the pubertal subgroup, mean height was lower in patients receiving additional amino acid mixture free of pathological precursor (AAM) than in those who did not: -1.22 (0.18) vs. -0.63 (0.16), p=0.0182. In the subgroup receiving AAM, the natural protein

intake expressed as percentage of recommended daily allowance, was lower than in the group that did not: 63.6 (22.1) vs. 90.4 (37.9), $p=0.0023$. Overall BMI Z-score was 0.4 (1.5) in early infancy, 0.5 (1.4) in prepubertal and pubertal subgroups. BMI Z-score was not different between patients with a height \leq -2DS and those with normal height. Body composition was performed in 55 patients aged 8 to 22.2 years. Mean Lean mass Index (LMI) z-score was -2.03 (1.15) and was significantly lower than Fat mass Index (FMI) (-0.44 [0.89], $p<0.001$). We found no difference in FMI or LMI between boys and girls.

Discussion: In this large cohort of IMD requiring a strict controlled protein diet, we found a growth retardation that progressively worsens from early childhood to puberty, leading to a final height lower than expected. Delayed puberty is frequent. Body composition in the pubertal subgroup showed a decreased LMI and a normal FMI despite normal BMI. One mechanism of growth retardation could be the lower amount of natural protein intake that is found in the pubertal subgroup. Further studies are required to confirm this hypothesis.

LB-12

Thyroid function in neonates conceived after hysterosalpingography with iodinated contrast media

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Objective: Hysterosalpingography (HSG) to assess patency of the Fallopian tubes with the use of iodinated (oil- or water-based) contrast media is a standard test during fertility work-up. An observational study found an increased risk of congenital hypothyroidism in neonates whose mothers were exposed to high amounts of oil-based contrast during HSG. Oil-based contrast contains

more iodine (480mg Iodine/ml) than water-based contrast (250mg Iodine/ml). We investigated whether preconceptional HSG with oil- or water-based contrast affects neonatal thyroid function.

Design: Retrospective data-analysis of an RCT (H2Oil trial) (Dreyer et al., 2017).

Materials and Methods: In the H2Oil trial, 1,119 women were randomized to receive HSG with oil-based contrast (Lipiodol[®]) ($n=557$) or water-based contrast (Telebrix Hystero[®]) ($n=562$). Of the 369 women who gave birth to a liveborn infant, 208 consented to be approached for future research. Thyroid function tests of their children were retrieved from the Dutch neonatal screening program, which includes the assessment of T4 in all newborns, followed by TSH only in those with a T4 level \leq -0.8SD score. Furthermore, amount of used contrast and time between HSG and conception were compared between the groups.

Results: Data were collected on 140 neonates conceived after HSG with oil-based ($n=76$) or water-based contrast ($n=64$). T4 SD score was -0.05 (IQR-0.5-0.5) in the oil-group versus 0.2 (IQR-0.3-0.9) in the water-group (p -value 0.12). None of the neonates had a positive screening result for congenital hypothyroidism.

The median amount of used contrast did not differ between the oil-group (9.0ml (IQR6.0-11.8)) and water-group (10.0ml (IQR7.5-14.0)) (p -value 0.43). Time between HSG and conception was comparable between the oil- and water-group (respectively, 2.3 months (IQR1.1-4.3) versus 2.1 months (IQR1.1-4.0), p -value 0.83).

There were 13 children with a T4 \leq -0.8SD score in the oil-group versus 7 in the water-group (RR, 1.5; 95%CI 0.7-3.6, p -value 0.32). All had a normal TSH value. The amount of contrast or duration between HSG and conception between neonates with a T4 \leq -0.8SD and \geq -0.8SD score in either group did not differ.

Conclusions: This study showed that preconceptional HSG with oil-based and water-based contrast did not affect thyroid function in newborns. Although our results suggest that the use of iodinated contrast for HSG is safe for the offspring, we advise to keep the amount of contrast as low as possible. Since data on maternal thyroid function was lacking, while the fetal brain relies on the mother during neurodevelopment, no inferences regarding neurodevelopment could be made.

LB-13

Gut hormones secretion across clusters of Metabolic Syndrome in obese prepubertal children

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Background: Metabolic Syndrome (MS) represent a common dysmetabolic state in obese children and adolescents. Although data in youth show a role of gut hormones in the risk of developing MS, no data are available during the prepubertal age, especially across clusters of MS.

Objective: Thus the aims of this study were to evaluate components of the MS in prepubertal obese children compared to controls and to characterize changes in GLP-1, Ghrelin and Obestatin concentrations in all obese subjects divided according to the clusters of MS.

Methods: A group of 90 obese prepubertal children (42Male/48Female) was recruited at the Obesity outpatient clinic in Chieti. All components of MS were characterized in all subjects and obese children were divided into three groups according to the number of components of MS (group 1: 30 obese without components of MS; group 2: 30 obese with 1 components of MS; group 3: 30 obese with 2 or more components of MS). A group of 30 healthy prepubertal age- and gender matched peers (17Male/13Female) was recruited as controls. Anthropometric and blood pressure (Systolic, SBP and Diastolic DBP) were determined. Fasting blood samples were collected and insulin, glucose, lipid profile, ALT, AST and gut hormones including GLP-1 concentration, Ghrelin and Obestatin were measured. Differences across the groups (group 1, 2, 3 and controls) were evaluated by Kruskal-Wallis test and post-hoc analysis was performed by Mann-Whitney test.

Results: Fasting glycemia and insulin, HOMA-IR, Triglycerides, SBP and DBP progressively increased and HDL progressively decreased across the groups of obese prepubertal children compared to controls, showing worse values in group 3. In addition, GLP-1 and Ghrelin values were progressively reduced and Obestatin progressively increased across the group of controls and obese subject with or without components of MS. Particularly, the higher was the number of components of the MS the more impaired was gut hormone concentration.

Conclusions: Components of the MS and gut hormones (GLP-1, Ghrelin and Obestatin) concentrations are impaired in obese prepubertal children. The close association between progressive alterations in gut hormones levels and increasing number of components of the MS might suppose a role of these hormones in the determination of metabolic risk.

LB-14

Prenatal smoke-exposure is associated with increased anogenital distance in female infants

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Background: Cigarette contains more than 4,000 toxins and is suspected of having endocrine-disrupting properties. Anogenital distance (AGD) is an important biomarker of fetal androgen exposure and intrauterine masculinization. There are limited number of studies examining whether AGD is affected by prenatal smoke-exposure. The aim of this study is to investigate the effects of maternal smoking during pregnancy on newborn infants' AGD.

Method: Fifty-six female and sixty-four male newborn infants from mothers who smoked during pregnancy were included in this study. The control group for each sex was selected from infants whose mothers had no active or passive (in either the household or the workplace) smoke exposure before or during pregnancy. Questionnaire data on maternal demographic characteristics and information about cigarette use were collected. We assessed

genital anthropometry which included AGD for both male and female neonates, and stretched penile length (SPL), penile girth for males within the first 48 hours after birth. In boys, AGD has been measured from anus to posterior insertion of the penis (AGDapp), scrotum (AGDas), and cephalad insertion of the penis (AGDap). In girls, AGD has been measured from anus to posterior insertion of the clitoris (AGDapc), base of the posterior fourchette (AGDaf), and the top of the clitoris (AGDac). AGD(app/apc) were also normalized according to birthweight (AGD/weight in grams), length (AGD/CRL in millimeters), and ponderal index [AGD/(weight in grams/CRL in cubic centimeters)]. Anogenital index (AGI) was calculated by dividing the AGDapp/apc by cube root of birthweight.

Results: Prenatal smoke exposure was associated with significantly increased weight-adjusted AGD in female infants at birth ($p = 0.03$). There was also a significant correlation between mothers' daily smoking rates and weight-adjusted AGD ($r = 0.27 / p = 0.03$). Fetal smoke-exposure was not associated with any AGD measurements, SPL and penile width in boys.

Discussion: A significant increase in weight-adjusted AGD in female infants exposed to maternal smoking may be an indicator of antenatal androgen exposure and may pose a risk for short and long-term endocrine and metabolic problems. In this context, more extensive studies are needed to explain the relationship between maternal smoking and AGD change.

Keywords: Anogenital distance, Fetal smoke-exposure, Androgenic effect, Endocrine disruptors

LB-15

Efficacy of 3-Monthly Compare to Monthly Depot GnRH agonist (Triptorelin Pamoate) in the treatment of girls with Central precocious puberty in Korea

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Background: Triptorelin depot is largely used to treat central precocious puberty (CPP) in children and currently 3 monthly depot was introduced. No Korean data are available on 3-monthly GnRH agonist treatment in central precocious puberty.

Aim: To compare the efficacy of Triptorelin 11.25mg 3-months depot with 3.75mg monthly depot in suppressing pubertal development from the beginning to 6 month and 1 year after the treatment of central precocious puberty.

Methods: A retrospective study of 89 patients with Central precocious puberty treated with Triptorelin pamoate from 2015 to 2018 was conducted in the pediatric endocrinology clinic of Korea University Medical Center, Korea. 50 patients out of 89 were treated with Triptorelin 11.25mg 3-monthly depot and 39 patients were treated with Triptorelin 3.75mg monthly depot. Level of serum LH, FSH and estradiol was analyzed to compare the level of suppression of hypothalamus-pituitary-gonadal axis of each depot. Pubertal score, height and bone age were evaluated at the beginning, after the 6 months and one year of both therapies.

Results: The baseline characteristics of patients treated with 3-monthly depot were similar to those of patients treated with monthly depot. A suppressed luteinizing hormone (LH) response (peak LH \leq 3IU/L) to the GnRH test at 6 months occurred in 93.3% and 100% of the cases in patients treated with 3-monthly and monthly depot respectively. At 1 year after treatment, a suppressed LH response occurred in 96.2% and 100% of the cases in patients treated with 3-monthly and monthly depot respectively. Pubertal development was slowed in both patients. Degree of bone age advancement was decreased from 1.85 ± 0.51 and 1.86 ± 0.52 at beginning to 1.66 ± 0.60 and 1.75 ± 0.59 in patients treated with 3-monthly and monthly depot for 6 months respectively and to 1.26 ± 0.47 and 1.60 ± 0.55 in patients treated with 3-monthly and monthly depot for 1 year respectively.

Conclusion: Triptorelin pamoate 11.25mg 3-monthly depot is an effective treatment in patients with central precocious puberty. The efficacy for slowing pubertal development and reducing bone age advancement appear similar to both monthly depot and 3-monthly depot.

LB-16

Associations between pituitary abnormalities and treatment response in children with growth hormone deficiency. First multicenter study in Portugal

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Background/Aims: Magnetic resonance imaging (MRI) is used to investigate the etiology of growth hormone deficiency (GHD). There is a close relationship between structural changes in the pituitary gland and clinical status.

We aimed to investigate the relationship between MRI findings and clinical symptoms and treatment response in children with GHD.

Methods: The study was conducted in nine Department of Pediatric Endocrinology of Portugal. The study group included GHD children treated for at least two years whose magnetic resonance imaging was available. Patients whom were small for gestational age, with clinical syndromes, chronic diseases or acquired GHD were excluded. Clinical presentation, hormonal status and first year growth response were compared between

patients with pituitary abnormalities and patients with normal MRI. Results are presented as mean \pm standard deviation score (SDS) unless stated otherwise.

Results: Three hundred and twenty-one children were included, of which 230 were male (67,6%). The mean age at the start of treatment was $9,68 \pm 4$ years. Additional hormone deficiencies were found in 44 (13%) of patients. Pituitary MRI showed alterations in 141 (43,9%) patients; several patients showed more than one abnormality: 100 had pituitary hypoplasia, 71 had thin stalk, 58 had ectopic posterior pituitary, 16 had empty sella and 31 had the triad ectopic posterior pituitary, pituitary hypoplasia/aplasia and stalk defects. Patients with pituitary abnormalities started treatment significantly earlier ($8,5 \pm 1,2$ years vs $10,61 \pm 3,7$ years; $p=0,000$) and they had a more severe clinical phenotype (height SDS $-3,26 \pm 1,2$ vs $-2,89 \pm 0,84$; $p=0,001$) than patients with normal MRI. A statistically significant increase was observed in the variation of height increase rate after one year of treatment between the two groups ($0,91 \pm 1,04$ vs $0,59 \pm 0,57$; $p=0,001$).

Conclusions: MRI is a useful tool in assessing GHD patients. The presence and type of hypothalamic-pituitary abnormalities provides valuable information regarding the likely severity of the GHD and predicting treatment response.

LB-17

Assessment of Urinary Podocalyxin as a Marker of Glomerular Injury in Obesity Related Kidney Disease in Obese Children and Adolescents compared to urinary Albumin-creatinine ratio

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Introduction: Epidemiological data suggest that obesity was associated with increased risk of renal injury in children.

Objective: To assess urinary podocalyxin in obese children and adolescents as a marker of obesity related kidney disease (ORKD) compared to urinary albumin creatinine (A/C) ratio as the standard marker of glomerular injury.

Methodology: This case-control study included 64 obese children between 8 and 12 years old with long standing obesity (≥ 5 years duration) in addition to 34 healthy age and sex matched controls. Cases with diabetes mellitus, chronic illness, glomerulonephritis or other renal diseases as well as patients with endocrinological or genetic causes of obesity were excluded from the study. Study population were subjected to **full history taking** including age, sex, obesity onset and duration, feeding habits, dietary history, exercise, family history of obesity, type 2 diabetes mellitus, hypertension or renal diseases as well as **thorough physical examination** including anthropometry (weight, height, waist circumference, hip circumference, body composition), blood pressure assessment, pubertal staging, signs of insulin resistance as acanthosis nigricans. Urine samples for A/C ratio and podocalyxin were collected from study population as well as blood samples for assessment of serum creatinine and fasting lipid profile.

Results: The current study included 30 males and 34 females with mean age of 10.66 (\pm 1.69) years, mean birth weight of 3.15 (\pm 0.57) kg and mean duration of obesity of 7.9 (\pm 2.5) years. Family history was positive for obesity in 75%, T2D in 48.4%, hypertension in 42.2% and renal disorders in 10.9% within the study group. Most of the cases had normal renal function tests (95.3%). However, many patients had hypercholesterolemia (85%), hypertriglyceridemia (92.2%). No statistically significant difference was found between cases and controls regarding urinary Podocalyxin ($p = 0.115$). However, urinary A/C showed a statistically significant difference between both groups ($p = 0.021$). No statistically significant correlation was detected between urinary podocalyxin and different study parameters. However, there was a statistically significant positive correlation between urinary A/C and weight SDS, BMI SDS, GFR as well as triglycerides. Obese children with microalbuminuria had a statistically significant higher waist-hip ratio and higher TG level compared to those with normal A/C ratio ($p = 0.034$ & 0.018 respectively).

Conclusion: Urinary A/C ratio was increased in obese children and correlated significantly with BMI, GFR and TGs. On the other hand, urinary podocalyxin was not a sensitive marker of ORKD in children.

LB-18

Exploratory case-control study on ACE2 expression in children with short stature

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Background: Short stature is one of the most common presentations to paediatric endocrinologists. It is estimated that despite all the exams, in 50–90% of cases, children are labeled as having idiopathic short stature. It has been recently reported that genetic ACE2 deficiency is associated with reduced body weight as well as with impaired gestational weight gain and fetal growth restriction in pregnancy. It has been argued that ACE2 deficiency, which is usually associated with an increase of tissue Angiotensin II, could be associated with uterine artery dysfunction. Based on these premises, the aim of our study was to evaluate whether there was a difference of ACE2 expression in children with short stature as compared to age-matched controls.

Methods: For this purpose we designed an exploratory case-control study aiming at recruiting consecutively 40 children with short stature (cases) and 40 controls presenting at the Endocrinology Service. After signing the informed consent to participating in the study, children underwent a medical visit and a fasting blood sampling. Peripheral blood mononuclear cells (PBMC) were isolated to extract mRNA for gene expression analyses. Sera were collected for protein measurements.

Results: Children with short stature presented with lower height and body weight as compared to controls. Our preliminary data show that children with short stature exhibited a significant

reduction of ACE2 gene expression, and a significant increase of ACE/ACE2 ratio in PBMC. This was associated with a modest increase of Angiotensin II/Angiotensin 1-7 ratio. Our multivariate analysis showed that across the groups ACE2 was independently associated with height but not with body weight.

Conclusions: Our results suggest that short stature is associated with ACE2 reduction, which could play a causative role in growth reduction through IGF-1-dependent as well as IGF-1-independent mechanisms.

LB-19

CDX2 polymorphism of VDR gene and lipid profile in patients treated for acute lymphoblastic leukemia during childhood

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Introduction: Vitamin D activity is controlled by its receptor (VDR). Increased risk of obesity and metabolic disturbances among certain VDR alleles has been proven. This study was conducted to assess the association between Cdx2 (rs11568820) polymorphism of VDR gene (genotypes: AG, GG) and genetic susceptibility to components of the lipid profile in survivors of acute lymphoblastic leukemia (ALL) treated during childhood.

Materials and Methods: The study group consisted of 81 survivors (31 girls) mean age 14,7y, at least 1 year after successful ALL treatment. Control group consisted of 61 participants (35 girls) mean age 14,6y. Lipid profile (triglycerides (TG), total cholesterol (TCH) and fractions (HDL, LDL)) and the VDR gene polymorphism were identified. The data were analyzed using the STATISTICA v. 13.0 package.

Results: GG genotype of Cdx. In study group the average values of: TCH 172,28 \pm 32,60; HDL 53,16 \pm 12,07; LDL 102,52 \pm 28,63; TG 82,70 \pm 35,95. The lower level of HDL (statistically significant ($p<0,02$)) and higher level of average value of LDL, TG (both not statistically significant $p>0,05$) were identified, comparing to control groups. Positive statistically significant ($p<0,05$) correlations between: the levels of TCH and HDL, LDL; HDL and TG, but not in a control group, were identified.

AG genotype of Cdx. In study group the average values of: TCH 154, 56 \pm 20,45; HDL 51, 69 \pm 8,78; LDL 90, 25 \pm 15,25; TG 64, 13 \pm 21,77. The average values did not differ significantly compared to the controls. Statistically significant positive correlations between: TG and TCH, LDL, but not in a control group, were identified. Significantly lower level of HDL have been found in study group compared to control group (52, 55 \pm 11,37 and 57, 10 \pm 11,63 ($p=0,02$)). In female group there was significantly higher level of HDL compared to males (51, 97 \pm 11,76 and 57, 41 \pm 10,94 ($p=0,005$)).

Conclusions: ALL's patients with the GG genotype of Cdx2 polymorphism of VDR gene are predisposed to disturbances in lipid profile. The studies may allow earlier implementation of prophylaxis of the metabolic syndrome and more effective

treatment of lipid disorders in this group of patients, which can reduce the number of late effects including cardiovascular diseases in the future.

LB-20**Introduction of flash glucose monitoring in children with Type 1 diabetes: experience of a single-centre in Spain**

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Flash glucose monitoring is now included in the Portfolio of Services of the Public Health System of Andalusia in Spain. We enrolled 145 paediatric T1D diabetes patients into a prospective, interventional study of the impact of the FreeStyle Libre system on HbA1c levels in this population, as well as additional measures of glycemic health, such as Time in Range (TIR) and Time Below Range (TBR). Subjects were trained in use of the FreeStyle Libre system at the start of the study.

Mean age (\pm SD) of patients was 11.4 (\pm 3.1) years and average duration of diabetes was 5.2 (\pm 3.2) years. Patients were treated either with continuous subcutaneous insulin infusion (CSII; n=26) or with multiple doses of insulin (MDI; n=119). Outcomes measurements were performed at initiation, at 1 month, at 3 months and at 6 months.

Stratification of patients based on metabolic control showed that those with a baseline HbA1c \geq 7.5% had a significant reduction in mean HbA1c at 3 months ($8.11 \pm 0.71\%$ vs $7.7 \pm 0.6\%$; p=0.04). In contrast, those with a baseline HbA1c < 7.5% showed a significant increase in HbA1c at 3 months ($6.75 \pm 0.48\%$ vs $6.98 \pm 0.69\%$; p=0.03). Stratification of patients by treatment type (CSII vs. MDI) shows a significant reduction in HbA1c in those on CSII from baseline at month 3 and at month 6 (p=0.032). Amongst patients with baseline HbA1c \geq 7.5% there was a significant reduction from baseline at 3 months with MDI therapy and this was very marked ($9.66 \pm 0.80\%$ vs $7.70 \pm 0.85\%$; p=0.04).

There was no significant change in TIR or in TBR < 70 mg/dL. This may be attributed to the fact that was no masked baseline and any changes would have occurred within two days of the first sensor wear. However, the frequency of Level 1 (< 70 mg/dL) and Level 2 (< 54 mg/dL) hypoglycaemia was lowest in subjects who scanned their sensors \geq 10 times per day. Data also indicate a reduction in the rate of Level 3 hypoglycaemia from 4.2 episodes to 0.2 episodes per 100 patients per year after introduction of FreeStyle Libre.

In summary, the FreeStyle Libre system is beneficial in paediatric subjects with T1D to reduce HbA1c. Additional investigation is required to identify which individuals are most likely to benefit from use of the FreeStyle Libre system.

LB-21**How can the occurrence of delayed elevation of thyroid stimulating hormone in preterm infants born between 35 and 36 weeks gestation be predicted?**

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Objective: We evaluated frequency and risk factors of delayed TSH elevation (dTSH) and investigated follow-up outcomes in the dTSH group with venous TSH (v-TSH) levels of 6–20 mU/L according to whether late preterm infants born at gestational age (GA) 35–36 weeks had risk factors.

Methods: The medical records of 810 neonates (414 boys) born at Seoul National University Hospital who had a normal neonatal screening test (NST) and underwent the first repeat venous blood test at 10–21 days post birth were reviewed.

Results: Seventy-three (9.0%) neonates showed dTSH, defined as a v-TSH level \geq 6.0 mU/L, 12 of whom (1.5%) were started on levothyroxine medication. A multivariate-adjusted model indicated that a low birth weight (LBW < 2,000 g), a congenital anomaly, and exposure to iodine contrast media (ICM) were significant predictors for dTSH (all p < 0.05). Among these 73 dTSH infants, all 5 infants with TSH levels \geq 20 mU/L began levothyroxine medication, and 6 of 16 infants with v-TSH levels of 10–20 mU/L were indicated for levothyroxine, regardless of coexisting risk factors. However, only 1 of 52 infants with v-TSH levels of 6–10 mU/L who had a congenital anomaly was indicated for levothyroxine. All healthy late preterm infants, including LBW and multiple births, with v-TSH levels of 6–10 mU/L exhibited normal thyroid function.

Conclusions: dTSH was detected in 9.0% and levothyroxine was indicated in 1.5% of infants born at GA 35–36 weeks, particularly those with a LBW, a congenital anomaly, or history of ICM exposure. Either levothyroxine or retesting is indicated for late preterm neonates with TSH levels \geq 10 mU/L regardless of risk factors. If healthy preterm neonates show v-TSH levels of 6–10 mU/L, a second repeat test may not be necessary; however, further studies are required to set a threshold for retesting.

LB-22**Two Novel Mutations of the Lhx3 Gene Associated with a Severe Phenotype Involving Endocrine, Nervous and Skeletal Systems**

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LHX3, a member of the LIM-homeodomain transcription factors family, regulates pituitary development in vertebrates and the maintenance of mature anterior pituitary cells. Nineteen mutations in LHX3 gene have been reported in HGMD database, in homozygous and compound heterozygous patients. The phenotype may present with pituitary dysfunction only or with syndromes involving also nervous and skeletal systems. The MRI images include aplasia or hypoplasia of pituitary, hypointensity resembling microadenoma, enlargement with hyperintense signal, while in 10% of cases MRI is normal. Heterozygous family members are unaffected.

Our patient is a girl, term born. AGA for weight and length. After birth the child presented a severe respiratory distress. Considering her condition of therapy-refractory hypotension, pituitary hormonal investigations were performed at one month of age and a condition of panhypopituitarism was confirmed. Replacement therapy with hydrocortisone, levothyroxine and growth hormone was started. Brain MRI showed a loss of the adenohypophysis enhancement after-contrast.

At 6 months a psychomotor delay and a short neck with abnormal head and neck rotation were evident. At 4 years a left hip dislocation was partially surgically corrected and at 11 years a definitive vertebral fixation surgery for a severe scoliosis was performed. Since she was 3 years old she used hearing aids and at the age of 9 a cochlear implant was applied. At 8 years a surgical correction of a right eye strabismus was also performed. Despite GH therapy the patient had poor growth at -2.5 SDS. At the age of 11 she reached the 3rd percentile probably due to the scoliosis correction surgery. At 12 years the girl started estrogen therapy and at 13 years of age she has now reached the 10th percentile with the bone age still delayed of 3 yrs. The parents have a silent phenotype.

The **NGS analysis** of genes known associated with panhypopituitarism pointed out two new variants of LHX3 gene (NM_014564), not described in literature so far: c.G641C (p.R214P) located in exon 5 of the gene, inherited from the mother, and c.G359A (p.C120Y) located in exon 3, inherited from the father. These SNPs are located in a mutational hot spot, established functional domain without benign variation; multiple lines of computational evidence support a deleterious effect on the gene or gene product.

We **conclude** that the two variants pointed out from our analysis are good candidates to explain the complex proband phenotype. We are planning a functional study to validate this hypothesis.

LB-23**Long-term safety and effectiveness of recombinant human growth Hormone in Korean pediatric patients with growth disorders: 7-year interim analysis from LG Growth Study**

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Objectives: This study aimed to evaluate the long-term safety and effectiveness of recombinant human growth hormone (rhGH) (Eutropin® Inj., Eutropin®Pen Inj., Eutropin®AQ Inj., and Eutropin®Plus Inj., LG Chem, Ltd.) based on the interim analysis of a 7-year accumulated data of the LG Growth Study (LGS) in Korean pediatric patients with growth disorders including growth hormone deficiency (GHD), Turner Syndrome (TS), idiopathic short stature (ISS), small for gestational age (SGA) and chronic renal failure (CRF).

Methods: The LGS, an open-label, multicenter (total 73 sites), observational study has begun in November 2011, and the data collected until February 2019 was used for an interim analysis. All adverse events (AEs) were reported for safety, and effectiveness was assessed by height velocity, height standard deviation score (SDS) and inulin like growth factor-1 (IGF-1).

Results: During the 7-year study, a total of 3,144 patients were enrolled, and 2,871 patients (male 52%, female 48%) were analyzed for safety. Of those patients, 1,853 (64.5%) had GHD, 426 (14.8%) were diagnosed with ISS, 348 (12.1%) were born SGA, 235 (8.2%) had TS and 9 (0.3%) had CRF. The mean age at the screening was 7.8 years and the mean treatment duration was 3.6 years. Adverse events (AEs) were reported in 894 (31.1%) patients, most AEs were mild, and 163 (5.7%) adverse drug reactions (ADRs) was reported by physicians including headache (0.9%), injection site pain (0.7%), scoliosis (0.6%), and hypothyroidism (0.3%). A total of 27 neoplasms were reported in 24 (0.8%) patients, most were benign and/or non-related to rhGH. When the effectiveness was assessed in 1,094 patients followed-up for 12 months, height velocity was 8.9 ± 1.9 , 8.7 ± 1.6 , 9.0 ± 1.6 , 7.3 ± 1.8 , and 8.3 ± 2.1 cm/year in GHD, ISS, SGA, TS and CRF patients, respectively. When 4-year follow-up effectiveness was assessed in GHD and TS patients, height SDS significantly increased from baseline to 4 years in GHD patients (from -2.9 ± 0.9 to -1.3 ± 1.1 , $p < 0.0001$) and TS patients (from -3.2 ± 0.8 to -2.2 ± 0.8 , $p < 0.0001$), respectively. Total IGF-1 SDS significantly increased (from -0.7 ± 1.1 to 0.8 ± 1.7 at 12 months, $p < 0.0001$) and maintained within 0 to 2 SDS throughout the study period.

Conclusions: The incidence of AEs was low, and rhGH therapy was well tolerated. During 4 years of rhGH treatment, significant improvement in height SDS was confirmed in Korean pediatric patients with GHD and TS.

LB-24**Abdominal adiposity and total body fat as predictors of cardiometabolic health in pre-pubertal and pubertal youth**

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Objective: We aimed to investigate the usefulness of abdominal adiposity and total body fat as predictors of cardiometabolic health, especially insulin sensitivity, in children and adolescents.

Methods: Participants were 479 children and adolescents with obesity (322 boys and 157 girls) aged 3 to 18 years attending the Children's Hospital at Zhejiang University School of Medicine (Hangzhou, China). Participants underwent a number of clinical assessments: anthropometry, sexual maturation, whole-body dual-energy x-ray absorptiometry (DXA) scan, carotid artery ultrasound, as well as an oral glucose tolerance test (OGTT). Insulin sensitivity was assessed using the Matsuda index. Participants were stratified into groups by sex and pubertal stage.

Results: Among the pubertal and pre-pubertal groups, Android/Gynoid ratio (A/G) was strongly associated with most parameters of glucose homeostasis assessed. In striking contrast with A/G, Total body fat percentage (TBF%) only associated with fasting insulin in pubertal boys. For liver function, A/G was significantly associated with ALT and AST in pubertal girls and it was mainly correlated with ALT in boys, while TBF% only have a poor correlation with ALT in pubertal boys. A/G did not show a clear correlation with lipid profile with boys, but it was significantly in pubertal girls. None of them had correlation with Blood pressure changes and abnormal thickness in left carotid intima-media in all groups except TBF% had a low correlation with CIMT in pubertal boys. For adverse cardiometabolic outcome, The 0.1 increase in A/G was associated with a 44% and 42% increase in the risk of impaired glucose tolerance in pubertal boys and girls. The same increase in A/G was associated with an increase of 25% of abnormal glycaemia among pubertal boys and with a greater 77% risk of hyperuricaemia in pubertal girls. Every 0.1 increase in A/G was associated with a 19% increase in the risk of NAFLD in boy groups. In marked contrast with A/G, TBF% was only predictive of NAFLD in pubertal boys (aRR 1.05), and was not associated with the likelihood of any of other cardiometabolic outcomes assessed, irrespective of pubertal stage or sex.

Conclusions: Our study shows that A/G ratio is significantly associated with most cardiometabolic risk factors, especially glucose metabolic, in both pubertal and pre-pubertal children and adolescents, while TBF% had almost none significant correlation with these factors. Abdominal obesity can be a good predictor of cardiovascular metabolic risk factors in Chinese children.

LB-25**Low Trabecular Bone Score in Children with Inflammatory Bowel diseases**

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Background: Trabecular bone score (TBS) is an emerging technology to assess bone microarchitecture of the lumbar spine. In adults, this score has been shown to be a significant predictor for osteoporotic fractures, independently of major clinical risk factors and bone mineral density (BMD), and is a recommended tool in the evaluation and management of osteoporosis, especially secondary osteoporosis. To date, only few studies evaluated TBS in the pediatric population. To the best of our knowledge, no previous study investigated TBS in pediatric inflammatory bowel diseases (IBD) patients.

We aimed to assess TBS in children with IBD and to evaluate correlations with clinical, laboratory and densitometric variables.

Methods: A retrospective study of TBS and BMD measurements by dual-energy X-ray absorptiometry (DXA) of children with IBD. Clinical, anthropometric and laboratory data were retrieved from the medical charts. Bone mineral apparent density (BMAD) was calculated for each participant.

Results: Thirty-five patients (age at diagnosis 12.6 ± 3.4 years, 22 males) were included. Mean BMD L1-4 z-score of the cohort was -1.160 ± 0.965 , mean BMD TBLH z-score was -0.486 ± 1.033 , and mean BMAD z-score was -1.17 ± 1.15 .

Mean TBS was 1.359 ± 0.090 , lower than expected in healthy children in the same age and gender (TBS SD = -0.378, $p=0.016$). TBS was significantly correlated with weight-SDS ($r=0.635$, $p<0.001$), body mass index (BMI)-SDS ($r=0.491$, $p=0.003$), and DXA measurements: lumbar spine bone mineral content (BMC) ($r=0.434$, $p=0.009$) and total body less head (TBLH) BMD Z-score ($r=0.434$, $p=0.009$). In a subgroup of patients ($n=13$) who performed the DXA scan close to the diagnosis of IBD, a negative correlation was found between TBS and fecal calprotectin at diagnosis ($r=-0.674$, $p=0.016$). A stepwise linear regression analysis identified BMI z-score as an independent predictor of TBS ($r^2=0.469$, $p<0.001$).

Conclusions: TBS of children and adolescents with IBD is lower than TBS of healthy children and correlates with BMI, BMC and BMD. This finding may likely reflect the deteriorative effect of IBD on bone microarchitecture.

LB-26**Dramatic clinical response to Lenvatinib in one pediatric patient with advanced metastatic papillary thyroid carcinoma**

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Papillary thyroid cancer (PTC) is the most common thyroid tumor in childhood and adolescence. Most of these patients are referred with locally advanced and/or distant disease at the moment of diagnosis. Whenever is possible, these patients should be offered a total thyroidectomy and radioiodine remnant ablation. However, this approach is not always possible to perform, becoming these tumors as unresectable. These critical cases could benefit from the neoadjuvant treatment with multikinase inhibitors (MKI), so the standard treatment could be performed.

Lenvatinib is a MKI recently approved in many countries around the world for the treatment of radioiodine refractory adult differentiated thyroid cancer. Seldom pediatric case reports have been reported.

Case report: Female patient, 10 y.o. with a PTC locally advanced and metastatic to the lungs, who required 3 liters of oxygen due to the respiratory failure caused by the miliary bilateral pulmonary disease, mistakenly treated as tuberculosis two months previously to be referred to our Hospital.

A large thyroid mass fixed to profound tissues was corroborated with a CT scan, which showed a large heterogeneous neck mass with multiple microcalcifications associated to multiple lymph nodes. Both lungs had multiple micro-nodular disease with interstitial involvement.

Total thyroidectomy together with lymph node dissection was planned, but the extensive local infiltration led to define the unresectability of the lesion and the surgery was only limited to a thyroid biopsy. The patient had to undergo respiratory assistance. Pathological examination confirmed the presence of a PTC with a rearrangement of RET-PTC3 oncogene.

Eight days after surgery, we decided to indicate the compassionate use of Lenvatinib. Three days later, the patient had a clinical improvement and 9 days post Lenvatinib initiation the patient was discharged from hospital with no need of oxygen supply.

We are planning a new evaluation to define thyroidectomy and then radioiodine treatment.

Conclusion: Lenvatinib could be a very useful neoadjuvant therapeutic tool in pediatric patients with PTC not amenable for conventional treatment.

LB-27**Does karyotyping and in situ hybridization from three different germ layers elucidate low bone mineral density in Turner syndrome?**

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Background: Turner syndrome (TS) is caused by a total or partial loss of one X chromosome. Typical features include short stature and primary amenorrhoea. In addition, decreasing trabecular bone mineral density (BMD) and increasing cortical BMD during puberty has been reported at the radius. As chromosomal aberration remains a probable cause of bone changes in TS, we aimed to elucidate whether the karyotype differs among the tissues originating from the three different germ layers and whether this is associated with BMD.

Methods: Twenty-nine girls with TS aged 6.0-18.3 years (median: 11.8) participating in our previous bone density study (implementing peripheral quantitative CT at the radius) had new karyotyping. In addition to classical cytogenetic and molecular (fluorescence in situ hybridization, FISH) karyotyping from lymphocytes (mesoderm origin), FISH from cells gained through buccal (ectoderm origin) and root of tongue (endoderm origin) smears was also performed. Fifty (cytogenetic) and 250 (FISH) nuclei were analysed, respectively. SHOX gene deletion was considered "complete" whenever Xp was missing and "partial" in mosaicism. Percentage of X monosomy was calculated from the proportion of cell line with 45,X.

Results: There were 14 girls with mosaicism (5 with normal karyotype and 9 with aberrant second cell line) and 15 girls with 45,X karyotype in the lymphocytes as assessed by cytogenetics. "Complete" SHOX gene haploinsufficiency was present in 18 girls (either 45,X or Xp deletion in both cell lines), whereas in 6 girls, the Xp deletion was "partial" due to mosaicism. One subject presented 45,X monosomy in lymphocytes but had 45,X/47,XXX mosaicism in buccal and root of tongue cells. The maximum difference in percent X monosomy among the three germ layers was 15-66 (mean 37±18). Whereas trabecular volumetric BMD (vBMD) was not associated with percent X monosomy in either of the germ layers, cortical vBMD was negatively associated with percent X monosomy in the lymphocytes ($\beta=-0.025\pm0.012$, $p=0.042$ for cytogenetics and $\beta=-0.028\pm0.013$, $p=0.048$ for FISH) but not in buccal ($\beta=-0.011\pm0.014$, $p=0.46$) or root of the tongue cells ($\beta=-0.013\pm0.012$, $p=0.32$).

Conclusions: The karyotype result in TS differs by the embryonic origin of the tissue sample. Despite that the entire skeleton develops from mesoderm, only the cortical bone compartment had a quantitative association with X monosomy in lymphocytes. Gradual decrease in trabecular vBMD during puberty must have non-genetic causes. Knowledge of the karyotype of all three germ layers may help elucidate other features of TS.

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The Volumetric Changes in the Olfactory Bulb Depend on Body Mass Index

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Background/Objective: Energy balance is preserved through the exchange between body weight and adipose tissue across the multi-faceted complex network that is composed of the sensorial, metabolic, and neuroendocrine circuits. Olfactory control of the process is maintained through the central structures that include the hypothalamic-pituitary axis, together with the interplay between the olfactory bulbus (OB) and adipose tissue. Although the interaction of the body mass index (BMI) with olfactory functions has been studied very well, there is no clear information about its relationship with OB volume (OBV). This study focuses on the relationship between OBV and BMI.

Methods: The children (n=184) were categorized according to their BMI percentiles with the groups being normal weight (n=89), overweight (n=26), children with obesity (n=26) and children with severely obesity (n=43). The OBV of all the children were calculated using magnetic resonance image.

Results: The means of the OBV were higher in children with a high body mass index (BMI) those with a normal weight. The OBV increased in overweight and children with obesity groups (59.49 ± 13.44 - 70.65 ± 13.62) but decreased in children with severely obesity (59.80 ± 17.28). In overweight and children with obesity groups, a weak positive correlation between the BMI and OBV were detected ($r_{26}=0.302$ - $r_{26}=0.288$), while in children with severely obesity group, a moderate negative correlation was detected ($r_{43}=-0.425$).

Conclusion: This study revealed that the there is a positive, albeit weak, correlation between OBV and BMI in children with overweight and obese, but the correlation, albeit moderate, inverted in the children with severely obesity. This finding may indicate interdependent variability between OBV and BMI.

Poster Category 2

Adrenals and HPA Axis

P2-1

Gender identity, sexual orientation and quality of life in women with non-classic congenital adrenal hyperplasia

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Context: Higher frequency of atypical gender identity, non-heterosexual fantasies and sexual relationships, and cross-gender role behavior has been reported in females with the more severe salt wasting form of congenital adrenal hyperplasia (CAH). Data on these aspects and quality of life (QOL) among the milder, more prevalent form, the non-classic CAH (NCCAH) is scarce.

Objective: To assess gender identity, gender role, sexual orientation and health-related quality of life (HRQoL) in women with NCCAH.

Design and Participants: Thirty-eight NCCAH females median age 34 years (range, 18-44) and 62 age-matched healthy female controls participated in this questionnaire-based study. Outcome measures included: The Multi-Gender Scale Identity Questionnaire (multi-GIQ), a Sexuality Questionnaire, the Personal Attributes Questionnaire and the World Health Organization Quality of Life (WHOQOL) questionnaire.

Results: Sociodemographic parameters including marital status, number of children, educational level and income were similar for patients and controls. The two groups were similar on most measures of the Multi-GIQ and those of the sexuality questionnaire. However, "sometimes-feeling-as-a-man"-and-"sometimes-feeling-as-a-woman" were more frequently reported in the NCCAH group compared to the controls [7/38 (18.4%) vs 3/62 (4.8%) respectively, $p=0.02$], and a higher percentage of NCCAH women reported first falling in love with a woman (11.1% vs 0%, $p=0.02$). There was no difference between the groups on any QOL measures.

Conclusion: Our findings suggest subtle differences in gender identity and sexual orientation between adult NCCAH females and controls. Quality of life was not impaired in subjects with NCCAH compared to controls. The impact of exposure to mildly elevated androgen levels during childhood and adolescence on the female brain warrants more in-depth assessment in further studies.

CYP11A1 (side-chain cleavage enzyme) defect in three brothers causing glucocorticoid and mineralocorticoid deficiency and development of testicular adrenal rest testicular tumour

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Background: CYP11A1 gene encodes the cholesterol side-chain cleavage enzyme, P450scc, which plays a key role in the initial steps of steroidogenesis. CYP11A1 insufficiency lead to a variable phenotype ranging from severe early onset primary adrenal insufficiency (PAI) in the neonatal period, with 46,XY DSD; to late-onset PAI with normal genitalia.

Objective: Detail the phenotype of a family sharing newly described compound heterozygous mutations¹ in CYP11A1, identified by HaloPlex targeted capture array.

Family study: This non-consanguineous Scottish family comprised unaffected parents and two sisters with three affected brothers (II-2, II-3 and II-5). Learning difficulties were present in the mother, II-2 and II-3. All siblings were born at term, birthweight 2.6 (II-2), 2.5 (II-3) and 2.8 kg (II-5). II-5 was diagnosed first aged 3.7 years following a number of "febrile" convulsions and was found to be hyperpigmented with sodium 129mmol/l, potassium 5.9mmol/l, renin 1209 µU/l (NR:9-50), ACTH 1089 mU/l (N<20), and basal/peak cortisol after synacthen 174/178 nmol/l. Assessment in II-2 and II-3 at 8 and 9 years showed that they too were deeply pigmented with normal electrolytes but high ACTH and renin; basal/peak cortisol 339/389 and 278/289 nmol/l. An X-linked disorder was considered likely, but DAX-1 and adrenoleukodystrophy studies were negative. Conventional glucocorticoid and mineralocorticoid replacement for unclassified PAI was given. All three brothers completed puberty- delayed in II-2 and II-3 with G2/G4-5 at 13.1/16.9 and 14.2/17 years. Genetic analysis during adulthood revealed compound heterozygosity of the CYP11A1 gene with an rs6161 variant (c.940G>A, p.Glu314Lys) affecting splicing and another disruptive variant causing frame-shift and premature stop codon (c.790_802del, K264Lfs*5)¹. At last review aged 32, 36 and 37 years the brothers were stable on hydrocortisone and fludrocortisone replacement, had scanty body hair but normal pubic hair, normal testicular volumes (15-20 ml), normal serum testosterone (27.2, 33.3 and 24.7nmol/L) but FSH values 41.2, 9.3 and 13.8 u/L. II-3 suffered from epilepsy and died shortly after from a prolonged convolution. II-5 had undergone orchidectomy for suspected malignancy aged 25 years with initial

histology reported as showing nodular Leydig cell hyperplasia, revised to testicular adrenal rest tumour (TART) when the diagnosis came to light.

Conclusion: Partial CYP11A1 defect is emerging as a surprisingly common cause of previously undiagnosed PAI. This kinship demonstrates the importance of studying other family members when PAI presents and of precise diagnosis, which could have identified TART as the cause of testicular enlargement thus avoiding orchidectomy in the younger brother.

Contraceptives in female adolescents with 21-hydroxylase deficiency (CAH) - a way to optimize treatment with respect to androgen excess? A pilot study

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Background: At present, treatment of „classic“ congenital adrenal hyperplasia (21-hydroxylase-deficiency, 21OHD) consists of glucocorticoid and mineralocorticoid replacement. However, often androgen excess and its negative metabolic impact are difficult to control without accepting glucocorticoid overtreatment, especially in adolescence. In healthy subjects oral contraceptives (containing ethinylestradiol) increase cortisol binding capacity and free cortisol, while prolonging half-life of unbound cortisol and reducing its clearance. Intake of combined contraceptives (ethinylestradiol/progestin) in healthy women leads to decreased androgen levels by inhibition of ovarian and adrenal androgen synthesis and by an increase of sex hormone binding globulin (SHBG).

Therefore we aimed to investigate the effect of contraceptives in female adolescents with 21OHD on androgen levels in a pilot study.

Methods: Retrospective chart analysis. Laboratory data of female adolescents with confirmed 21OHD under glucocorticoid and mineralocorticoid treatment were reviewed before and after introducing an oral or transdermal contraceptive: Serum 17-OH-progesterone-, androstendione-, DHEA-, DHEA-S- and free testosterone-values were measured basally and 3-6 months after introduction of the contraceptives.

Results: So far, five adolescents with available data sets could be identified in our centre. Mean age was 15.5 years [range 14.2 – 17.2]. Four patients took hydrocortisone, prednisolone and fludrocortisone as their long-term medication, one patient hydrocortisone and fludrocortisone. The oral contraceptives (4 patients) contained ethinylestradiol 0.03-0.035 mg or cyclic (1, 2 and 3 mg) estradiol valerat and either levonorgestrel, cyproteronacetat, dienogest or desogestrel. The transdermal preparation consisted of ethinylestradiol 0.6 mg and norelgestromin 6 mg. Comparing laboratory values basal to values under treatment with contraceptives a significant decrease of androgens androstendione, DHEA, free testosterone (all p <0.05) was observed. No difference was seen for 17-OH-progesterone or DHEA-S. Treatment regimen changes for hydrocortisone were thus executed in two patients.

Conclusion: In this pilot study in five young females with classic CAH due to 21OHD, we saw a significant reduction in serum androgens after introduction of contraceptives. We therefore plan to confirm this promising result in a larger multi-centre cohort study with a prospective design looking at clinical and biochemical parameters under use of contraceptives. Steroids will be measured from serum and urine by mass spectrometric methods, and hydrocortisone needs calculated. Markers of metabolic syndrome will also be assessed.

P2-4

Bone age advancement in prepubertal children with premature adrenarche

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Introduction: Premature adrenarche (PA) is usually defined as the appearance of clinical signs of androgen action before the age of 8 years in girls and 9 years in boys, associated the serum DHEAS above 40 μ g/dL.

Aims: 1) To characterize a population of prepubertal children with PA regarding birth weight, anthropometry, growth velocity, height difference, bone age, IGF1 and DHEAS. 2) To compare IgF1, bone age, growth velocity and height difference in normal-BMI and overweight/obese PA children. 3) To correlate bone age advancement, DHEAS, BMI and IGF1 in this population.

Methods: Cross-sectional study of 44 children with PA (37 girls/7 boys), with a mean age of 7.5 \pm 1.1 years-old.

Data was collected from their healthy card regarding gestational age and birth weight.

Anthropometric evaluation and Tanner staging was performed by a trained observer. Weight, height and BMI were converted to SD (WHO charts). Growth velocity was converted to SD (Tanner height velocity charts). Bone age was evaluated by a single endocrinologist (Greulich-Pyle).

Target height was calculated from parents' height. Predicted height was assessed with the Bailey-Pinneau method. Height difference was defined as the difference between predicted height and target height.

In all children, IGF1 (converted to SD according to age/gender/Tanner stage) and DHEAS were evaluated.

IGF1, bone age, growth velocity and height difference of normal-BMI PA children were compared to those of overweight/obese children, using independent samples t test.

The correlation between bone age advancement and DHEAS, BMI and IGF1 was performed using Pearson's correlation.

Results: Mean birth weight was -0.285 \pm 1.1SD. At prepuberty, 43% (19) had a normal BMI and 57% (25) were overweight or obese. Mean height was 0.96 \pm 0.93 SD. Mean height difference was 2.1 \pm 6.7 cm. Mean growth velocity was 1.4 \pm 1.8 SD. Mean bone age advancement was 1.1 \pm 1.1 years. Mean IGF1 levels were 2 \pm 1.4 SD. Mean DHEAS was 121 \pm 58 μ g/dL.

Overweight/obese children had higher IGF1 levels ($p=0.026$) and presented a more advanced bone age ($p=0.044$) than normal-BMI children.

Bone age advancement was correlated with DHEAS ($r=0.449$; $p=0.05$) and IGF1 ($r=0.342$; $p=0.015$), but not with BMI.

Conclusion: Accordingly to previous knowledge, overweight and obese children present high levels of IGF1 and advanced bone age. In this particular group of PA children, there is an adrenal hyperfunction (higher levels of DHEAS) that seems to be more expressive in overweight and obese children and possibly contributes to a more rapid skeletal maturation.

P2-5

Clinical phenotype and genotype association in patients with 21-hydroxylase deficiency

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Introduction: Congenital adrenal hyperplasia (CAH) is an autosomal recessively transmitted disease and 95% of CAH cases are due to 21-hydroxylase deficiency (21-OHD). There are more than 100 mutations that cause CAH due to 21-OHD and the clinical expression of the disease is reported to correlate with mutated alleles.

The aim: The aim of this study was to investigate responsible mutations and then to evaluate genotype-phenotype relationship in CAH patients with 21-OHD.

Methods: Mutations were firstly investigated by sequence analysis by Sanger method; when needed Multiplex Ligation-dependent Probe Amplification (MLPA) technique was applied. Mutations were grouped as of group 0, A, B or C and compared with the expected clinical phenotype i.e. Group 0: Salt wasting (SW), Group A: SW, Group B: Simple virilizing (SV), Group C: Nonclassical (NC) and positive predictive value (ppv) was determined for the different groups (1).

Subjects: Genotype was investigated in 40 cases with 21-OHD (33 classical, 7 nonclassical).

Results: Responsible mutations were determined in 37 of the cases (n:15 SW, n:15 SV, n:7 NC). The rate of parental consanguinity was 43.2%. In 4 compound heterozygotes genotypes were determined after the genotyping of parents. In 11 cases only Sanger method, in 26 cases Sanger and MLPA methods were used. Mutations were identified in 73 alleles from 37 cases (mutation only in one allele in one case: Deletion/Not detected). The most common mutation was IVS2-13A/C>G (28.3%), followed by p.I172N mutation (17.5%) and large gene deletions (14.7%). In addition, heterozygosity for p.Y59N mutation which has not been previously reported in our region and a higher rate (10.8%) for the p.V281L mutation than that reported before was found.

In group 0, ppv was 72% (8 SW, 3SV); in group A, ppv was 50% (6 SW, 6 SV); in group B, ppv was 85% (6 SV, 1NC); in group C, ppv was 100% (6/6 NC). Deletion/Not detected was not included.

Conclusion: In our study group, genotype-phenotype correlation was found to be less in simple virilizing CAH than salt wasting and non-classical types of CAH.

Reference

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P2-6

Corticosteroid Use: Practices and Attitudes of Pediatricians

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Context: Synthetic corticosteroids are medications frequently prescribed for a wide range of medical indications. Various preparations differ in their biological effect, mode of administration, potency and duration of action. Comprehensive knowledge is essential in order to prescribe corticosteroids in an efficient yet safe manner.

Objectives: To explore pediatricians' practices and attitudes regarding corticosteroid administration and to determine whether intraprofessional practice gaps between general pediatricians and subspecialists exist.

Design, Participants and Methods: A cross-sectional, nationally representative, web-based survey was disseminated to Israeli registered board-certified pediatricians between February 4th and July 31st, 2018. The Pediatricians Corticosteroids Survey was generated in accordance with recommended survey methodology. Relevant items were developed through literature reviews and in-depth interviews with pediatricians from different disciplines at Dana-Dwek Children's Hospital. The items were grouped into domains: (A) demographics (B) corticosteroid prescription and (C) corticosteroid knowledge [subscores - 'corticosteroid potency and half life' maximum score of 7, 'tapering-down' and 'stress dose' each maximum score of 6, maximum total score of 19]. One-way ANOVA was used to analyze survey outcomes and post hoc analysis (Tukey HSD test) was performed. Cronbach's alpha coefficients were 0.76 (domain B) and 0.83 (domain C) demonstrating internal consistency.

Results: 349 pediatricians (45.8% males) responded and completed the survey, 76.5% studied medicine in Israel; 207/349 (59%) had a pediatric subspecialty, 37/349 (10.6%) were pediatric endocrinologists. The responders were highly experienced

physicians: 58% had over 10 years of pediatric clinical experience and 57.7% treat on average more than 60 patients per week. Nearly half of the responders (47.5%) estimated they prescribed corticosteroids to 10-30% of their patients and 7.5% to over 30% of their patients. Despite vast experience with corticosteroid usage, 4.1% responded 'not sure' when 'tapering of' steroids is required, 8.3% responded 'not sure' what 'stress dose' refers to and 10.1% responded 'not sure' when stress dose is required. Pediatric endocrinologists scored higher on all knowledge-based items compared to general pediatricians and other subspecialists (mean total score: 11.25±2.49 vs. 7.94±2.61 vs. 6.95±2.67, p<0.001 and in each of the subscores, p<0.001). Overall, 96.2% of respondents felt it would be helpful to participate in continued medical education sessions.

Conclusions: Substantial intraprofessional practice gaps exist between pediatric endocrinologists and general pediatricians and other subspecialists in both corticosteroid prescription practice and knowledge. Continued medical education programs on the topic of corticosteroids are warranted to improve clinician competence and performance and patient outcomes.

P2-7

Updates on genotype and phenotype of Vietnamese Patients with X-Linked Adrenoleukodystrophy

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Background: The X linked adrenoleukodystrophy (X-ALD) is a peroxisomal disease caused by defects of the *ABCD1* gene on chromosome Xq28. This disease is characterized by progressive neurologic dysfunction, and occasionally associated with adrenal insufficiency. The estimated frequency is about 1:42000 in male, whereas the estimated frequency for heterozygous women is 1:14000. There was no correlation between genotype and phenotype of X-ALD patients.

Objective: To describe phenotype and genotype in affected male patients in Vietnamese patients with X-ALD.

Method: This is case series study. Clinical features, biochemical finding, cerebral MRI lesions and genetic testing of 23 cases from 20 unrelated families were studied.

Results: Age of onset was between 1.5 and 14 years. Most of patients had symptoms including cognitive impairment, extrapyramidal signs and/or hyperpigmentation, adrenal crisis, low serum cortisol levels, and increased plasma ACTH levels. Neuroimaging studies (cerebral MRI) showed classical patterns in all patients with neurological symptoms. Cerebral ALD has worse prognosis, high mortality rates. We identified 19 different causative mutations of *ABCD1* in 23 patients including missense mutations (13/19), deletion (4/19), nonsense mutation (1/19) and splice site mutation (1/19). Of which, eight novel mutations in six unrelated patients including c.1202G>T (p.Arg401Trp); c.1208T>A (p.Met403Lys); IVS8+28-551bp del; c.1668G>C (p.Gln556His); c.292_296delTCGGC (p.S98RfsX95); c.1946_1947insA (p.Asp649fsX733), c.46-53del insGand the extent of deletion included between IVS1+505 and IVS2+1501,

containing whole the exon 2 (4243bp), plus insertion of 79bp from BAP31 and 8bp from unknown origin in this deleted region were identified. But we did not clarify the genotype – phenotype correlations.

Conclusion: Children with X-Linked Adrenoleukodystrophy should be performed mutation analysis which helps in making diagnosis and treatment decision. We should do genetic testing for patient's family member, especially female to diagnosis female affected. Families of children with X-ALD should be given genetic counseling.

P2-8

Novel TBX19 Mutation as Cause of Hypoglycemia in Two Siblings

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We describe a female neonate born from consanguineous parents who presented at birth with respiratory distress and severe hypoglycemia. At six months of age, the child was admitted to the Intensive care Unit because of two critical episodes characterized by fever and loss of consciousness. Child condition were critical and suggestive of sepsis, but blood tests showed severe hypoglycemia (19 mg/dl), hyponatremia (Na 132 mmol/l), compensated metabolic acidosis and increased inflammatory markers (CRP 209 mg/l, normal value <5, PCT 32.6 ng/ml, n.v. <2). During the hypoglycemia episode, endocrine analyses revealed low levels of ACTH (<5 pg/ml), cortisol (<1 mcg/dl) and basal GH (2.22 ng/ml), but normal thyroid hormones. The magnetic resonance imaging of brain and of the pituitary gland showed normal morphology. After diagnosis of central hypocortisolism we immediately started her on substitution therapy with hydrocortisone. During the follow-up the infant showed decreased growth velocity which was diagnosed as GH deficiency on the basis of low GH levels in response to arginine (GH = 4.21 ng/ml) and low IGF-1 levels (<25 ng/ml). At 14 months of life she was started on GH therapy. After two years, a second child was born in the same family: he presented at three hours of life with profuse sweating, severe hypoglycemia and persistent vomiting. Because of the family history, we performed blood tests which revealed isolated central hypocortisolism (ACTH <5 pg/ml, serum cortisol <1 mcg/dl), while basal GH, thyroid hormone levels and magnetic resonance imaging of brain and pituitary gland were normal. We started him on substitutive therapy with hydrocortisone with quick improvement of his clinical condition. Genetic analysis of the two siblings by using a specially constructed NGS panel revealed a novel homozygous mutation of TBX19 gene (c.269 T>C (Leu>Pro) of exon 2) in both of them and as heterozygous in their parent. Biallelic mutations of this gene are associated with congenital ACTH deficiency. This mutation, not previously described, affects a highly conserved region of the protein, and was reported as probably damaging suggesting that is most likely causative of the central hypocortisolism described in the two brothers.

P2-9

The clinical polymorphism and variability of X-linked adrenoleukodystrophy in one Russian family

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Adrenoleukodystrophy is an X-linked, inherited metabolic disorder. Here, we present 3 clinical cases of different phenotypes with one mutation in *ABCD1* gene in one family.

Patient 1: At the age of 9 years, manifestation of neurological symptoms was observed, skin color changed, these symptoms progressed monthly. MRI of the brain showed 13 points on Loes scale.

During the examination, the diagnosis of X-linked adrenoleukodystrophy was suspected; it was confirmed by biochemical (elevation of very long chain fatty acids - VLCFA) and molecular genetic studies (a mutation in exon 1 of the gene *ABCD1* (c.871G>A (p.Glu291Lys) in the hemizygous state). The child was diagnosed with X- linked adrenoleukodystrophy, childhood cerebral form, primary adrenal insufficiency, and hormone replacement therapy was prescribed. Six months after the manifestation of the disease the child died.

Patient 2: at the age of 1 year 4 months the boy stopped sitting down, was constantly sleeping, was sluggish. Considering the diagnosed disease in the middle brother, a molecular genetic study was performed, and an identical mutation in the *ABCD1* gene was detected. During the examination, primary adrenal insufficiency was diagnosed, hormone replacement therapy was prescribed. Up to 4 years of age during dynamic observation there were no changes in the nervous system, according to MRI of the brain, there were no pathologies. Currently, the boy has X-linked adrenoleukodystrophy: Addison's disease only.

Patient 3, 14 years: At the time of the examination, there were no complaints. There have never been clinical signs of adrenal insufficiency and neurological symptoms.

The diagnosis of X-linked adrenoleukodystrophy was confirmed by elevation of VLCFA and the presence of a mutation in the *ABCD1* gene, as in younger brothers. During ACTH stimulation test (with cosyntropin), cortisol was increased up to 1173 nmol/l.

Sex hormones correspond to puberty stage (Tanner 3).

Given the prolonged absence of primary adrenal insufficiency and the absence of neurological manifestations, the boy may have an asymptomatic X-ALD phenotype.

Conclusion: There is no correlation between the genotype and the phenotype. In this family, the presence of 3 forms of the disease is noted: childhood cerebral form, Addison's disease only and asymptomatic phenotype. However, progression of the disease is possible; patients require medical follow-up. Factors affecting the development of one form or another are currently unknown.

P2-10**Functional adrenocortical oncocytoma – a rare cause of progressive virilization and secondary amenorrhea**

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Introduction: Oncocytomas are rare epithelial tumors that can be found in various tissues such as kidney, salivary and endocrine glands. Adrenocortical oncocytomas (AON) are very rare tumors with around 160 patients described in the literature. Generally they are regarded as benign and mostly hormonally nonfunctional. When hormonally active, these tumors produce adrenal steroids resulting in various clinical presentations such as virilization, feminization, and Cushing or Conn syndrome. Until now, only 8 pediatric patients with functional adrenocortical oncocytomas (FAON) have been described in literature.

Case Report: We report on a 15.5 year old girl referred for secondary amenorrhea lasting 8 months. Slowly progressive virilization was reported for almost 2 years. At presentation she had deep voice, acne, hirsutism (Ferriman-Gallwey score 22), clitoromegaly and atrophic breasts. Blood pressure was normal. Initial laboratory findings revealed marked hyperandrogenemia: testosterone 17.7 nmol/L (ref. 0.4-1.7), androstenedione 21.8 nmol/L (ref. 1-12), DHEAs 26.8 umol/L (ref. 2-10), with suppressed LH 0.1 IU/L, FSH 0.3 IU/L and estradiol 92 pmol/L. Serum and urinary cortisol as well as aldosterone and plasma renin activity were normal. Abdominal CT scan showed right adrenal gland mass measuring 4 cm in diameter. Subsequently laparoscopic right adrenalectomy with lymphadenectomy was performed. Pathohistological diagnosis revealed oncocytic adrenocortical tumor with benign characteristics according to Wieneke criteria and Bisceglia classification. Adrenal androgen levels normalized completely after the surgery and the girl regained menstruation 1.5 month following tumor extirpation.

Conclusion: In conclusion, AONs are very rare tumors with yet unidentified pathogenesis and potential risk factors for their development. They are mostly discovered in adults, but can also be found in children. There is no specific age distribution in children with FAON.

Unlike adults, all children with FAON presented with right sided adrenal mass and very strong female preponderance (8/9). Most of the patients with FAON (7/9), including our, presented with symptoms of androgen excess. All but one were pathohistologically classified as benign at the time of diagnosis. Follow-up time ranged from 1-84 months in children with FAON. None of them had signs of disease recurrence at that time.

Due to extreme rarity of this tumor in children and no clear evidence regarding its' true potential, long-term follow-up of these children should be recommended.

Since there are no specific guidelines regarding management of these patients, knowledge assembled from individual cases would provide better understanding.

P2-11**Long-term Prednisone versus Hydrocortisone Treatment in Children with Classic Congenital Adrenal Hyperplasia (CAH): A Controlled Study**

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Background: Debate still exists about the safety of long-term use of prednisone (PD) versus hydrocortisone (HC) for treating children with CAH. Relatively slight supraphysiologic levels may be enough to blunt growth velocity, increase weight gain.

Objectives of the study: We evaluated the anthropometric and biochemical effects of long-term PD versus HC treatment in children with CAH-21OHD.

Patients and Methods: We studied 30 children with classic CAH (19 females and 11 males), 22 were on PD (n= 22) or 8 were on HC treatment, since their first diagnosis. Clinical data included age, gender, duration of therapy, dose of HC and or equivalent dose of HC in the PD group, blood pressure, height (Ht) and weight. Ht-SDS and BMI were also calculated. Biochemical data included measurement of 17-OH progesterone, cholesterol, triglycerides (TG), HDL, LDL, fasting glucose, and insulin concentrations. HOMA-IR was calculated. Carotid intima-media thickness (CIMT) was measured using high-resolution B-mode ultrasonography. Thirty normal age-matched children were used as controls for the anthropometric and CIMT data.

Results: The age of children and duration of treatment did not differ among the two treatment groups. After a mean of 6 years of treatment, the Ht-SDS and BMI did not differ between the three groups of children. The equivalent hydrocortisone dose of children on prednisone was significantly higher than the dose for the hydrocortisone group. Both systolic and diastolic blood pressures (BP) of children on prednisone was slightly higher compared to those on HC group. However, the BP of the 2 treatment groups was not different compared to control children. Fasting blood glucose, HOMA-IR, plasma TG, HDL, and cholesterol did not differ among the two treatment groups. LDL levels were significantly higher in the PD group versus the HC group. The CIMT did not differ among the two treatment groups but was significantly higher in the treated groups versus controls. There was a significant linear correlation between BMI-SDS and CIMT ($r = 0.37$, $p = 0.047$).

Conclusions: Children with CAH-21OHD who were kept on PD therapy for 6.4 ± 2.7 years have maintained a normal linear growth. No difference in BMI, HOMA-IR, or CIMT was detected among the two treated groups. The efficiency, safety and convenience of a single daily dose of PD could be a good and relatively safe alternative to HC for the continuing treatment of CAH children. More prospective studies across childhood and adolescence are necessary to draw definitive conclusions.

P2-12**A case of X-linked adrenoleukodystrophy presenting with primary adrenal insufficiency and normal VLCFA**

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Introduction: X-linked adrenoleukodystrophy (X-ALD) is a rare autosomal recessive neurodegenerative disease caused by a mutation in the *ABCD1* gene. Although its clinical presentation varies, X-ALD is generally characterized by progressive demyelination of the central nervous system, primary adrenal insufficiency, and elevated plasma very long-chain fatty acid (VLCFA) levels. Herein, we aimed to present a case of X-ALD with normal VLCFA caused by a pathogenic variant in *ABCD1* gene.

Case: Twelve years seven months old boy was referred to our department because of hyperpigmentation, weakness, downward trend in his school performance since last year. He was born with birth weight of 1,750 grams at 32 gestational weeks after uneventful pregnancy. His neuromotor milestones were normal. The parents were no relatives. Two of his cousins were followed by another center due to adrenal insufficiency. In his physical examination, height was 165.6 cm (1.32 SDS), weight was 46.2 kg (-0.16 SDS), body mass index was 16.9 kg/m² (-0.99 SDS), blood pressure was 110/70 mmHg (50th centile), and his puberty was compatible with Tanner Stage 4. Muscle strength was 5/5 and hyperpigmentation was observed in his oral mucosa and nipples. In the laboratory examination, sodium 139 mEq/L, potassium 4.4 mEq/L, chloride 106 mEq/L, glucose 96 mg/dL, ACTH >1250 pg/ml, cortisol 3.8 µg/dL, aldosterone 66 pg/ml (N: 82-192), plasma renin activity 2.01 ng/ml/s (N: 0.5-3.3). Complete blood count, thyroid functions, lipid profile and gonadotropin levels were normal. The diagnosis of primary adrenal insufficiency was established and hydrocortisone was started (15 mg / m² / day). VLCFA examinations were found to be normal [C22: 32 mg / L (N: 10.5-51), C24: 28 mg / L (N: 8.5-37.5), C26: 0.3 mg / L (N: 0.1-0.6), C24 / C22: 0.83 (N: 0-1.16), C26 / C22: 0.01 (N: 0.02)]. Cranial T2A-FLAIR A MRI revealed bilateral hyperintense areas in parieto-occipital white matter. Genetic analysis of *ABCD1* revealed a hemizygote pathogenic variant in exon 6 that was previously reported [NM_000033:c.1571G>A(p.Trp524*)]. Family screening is planned. Recently, the patient is followed by pediatric metabolism and pediatric neurology clinics.

Conclusion: In patients with primary adrenal insufficiency, X-related adrenoleukodystrophy should be considered in differential diagnosis even if plasma VLCFA levels are normal. *ABCD1* gene analysis should be considered in the presence of clinical suspicion and radiological findings.

Key Words: Primary adrenal insufficiency, adrenoleukodystrophy, *ABCD1*.

P2-13**Different Potent Glucocorticoids, Different Routes of Exposure but The Same Result: Iatrogenic Cushing's syndrome and Adrenal Insufficiency**

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Background: Cushing's syndrome (CS) is very rare in children and the most common cause is the high doses of glucocorticoids (GC) administered. It is well known that application of potent GCs cause iatrogenic CS (ICS) due to suppressing hypothalamo-hypophyseal-adrenal (HPA) axis and later even adrenal insufficiency (AI). Other side effects of GCs are also seen in these patients.

Objective: The aim of this study is to review the clinical and laboratory findings of patients with ICS and to review other side effects.

Methods: Patients who were exposed to oral or topical long-term steroids were included in the study. Fasting serum biochemical values were obtained. Low-dose mcg ACTH test was performed in 12 patients. Hydrocortisone (HC) was started in patients with adrenal failure. After discontinuation of HC, Low dose-ACTH test was performed again. Abdominal ultrasonography was performed. All data was obtained from the hospital files.

Results: 14 patients (5 male) with ages ranging from 0.19 to 12 years were included in the study. The duration of GC exposure ranged from 1 to 72 months. Four patients had oral GC exposure, rest of them have topical GC exposure.

One patient was exposed to prednisolone, five to methylprednisolone, three to diflucortolone valerate, and four in clobetasol propionate. One infant used a cream for diaper dermatitis that was claimed to be herbal. Infant's blood steroid analysis revealed that all the endogenous steroids were suppressed. The equivalent daily dose (EDD) of the exposed GCs according to hydrocortisone was calculated in five patients (93±78 mg/m²/d). However, the EDD could not be predicted for those exposed to topical steroid.

At the admission BMI-SD was 1.82±2. Basal ACTH was median 16.9 (22-91) pg/mL and cortisol was median 3.73 (6.37) µg/dL. Stimulated cortisol was 8.55±6.5 µg/dL. Of the 14, 11 had AI and 2 infants had hypercalcemia. 25OHD3 was low-normal and PTH had been suppressed in these infants and, they also have nephrocalcinosis. Of 11 patients USG revealed five patients have hepatosplenomegaly. The HPA axis returned to normal at median 60 (160) days.

Conclusion: In this series, the 70% of the patients with life-threatening adrenal insufficiency and hypercalcemia were all infants. This result showed us that potent GCs cause serious side effects especially in infants. Physicians should be aware of the possible misuse of GCs and herbal products with the possibility of containing synthetic glucocorticoids because, parents are not informed of the side effects of these drugs.

Differences between normal-BMI girls with Premature Adrenarche and overweight or obese girls with Premature Adrenarche

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Introduction: There seems to be an undoubting, but still puzzling, relationship between obesity and premature adrenarche (PA).

Aim: To characterize a population of prepubertal girls with PA and to compare girls with a normal body mass index (BMI) with girls who are overweight or obese, in what regards gestational age and birth weight, age at the referral, clinical signs, anthropometry, bone age and hormone profile.

Methods: Cross sectional study that included 83 Caucasian prepubertal girls, with a mean age of 7.2 ± 1.2 years, who were followed in the Pediatric Endocrinology outpatient clinic of a university hospital in Portugal because of PA.

Data regarding gestational age and birth weight were collected from the child's health card. Parents' height and maternal age at menarche were self-reported. Clinical files were also reviewed. All subjects included in the study underwent anthropometric and clinic evaluation by a trained observer. All of them underwent bone age evaluation (Greulich Pyle comparative method) and blood collection for DHEAS, androstenedione, total testosterone and 17-hydroxyprogesterone.

Girls were then divided in two groups, according to their BMI SD (World Health Organization criteria): 1) normal BMI ($BMI \leq +1$ SD) (n=33); 2) overweight/obese ($BMI > 1$ SD) (n=50).

Results: Overweight or obese girls with PA had a slightly higher birth weight than normal-BMI PA girls (3075 ± 545 vs 2707 ± 834 grams; $p=0.024$; -0.05 ± 0.8 vs -0.64 ± 1.0 SD according to Fenton growth charts; $p=0.005$). No difference was found regarding gestational age, age of pubarche or maternal age at menarche.

Overweight or obese PA girls were taller (height SD 1.3 ± 1.0 vs 0.4 ± 1.1 ; $p=0.008$) and had a higher difference between height SD and target height SD (1.3 ± 0.8 vs 0.6 ± 1.1 ; $p=0.006$). No statistically significant differences were found in growth velocity or bone age advancement between groups.

Overweight or obese PA girls had higher levels of median total testosterone (0.045 vs 0 ng/mL; $p=0.015$) and median basal 17-hydroxyprogesterone (1.1 vs 1.0 ng/dL; $p=0.041$). No difference was found in DHEAS or androstenedione levels.

Conclusion: When compared with their normal-BMI PA peers, PA girls that are overweight or obese at prepuberty present higher levels of total testosterone and 17-hydroxyprogesterone. Therefore, we believe that obesity is a risk factor for hyperandrogenism since prepubertal years.

Rare Causes of Primary Adrenal Insufficiency at King Faisal Specialist Hospital -Retrospective Study

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Introduction:

- Adrenal insufficiency is a rare, but potentially fatal medical condition¹
- In children, the cause is most commonly congenital adrenal hyperplasia (**CAH**) but in recent years a growing number of causative gene mutations have been identified resulting in syndromes that share primary adrenal insufficiency (**PAI**) characteristics.
- PAI Incidence in Europe reported PAI 82–144/million²
- Higher CAH incidence has been reported in Saudi Arabia (1/7908) and 44 cases have reported for other causes³
- Underline causes for a lot of cases have not been identified till Whole exome sequencing have been applied.

Objectives:

- Primary: To Identify Causes for primary adrenal insufficiency at KFSHRC.
- Secondary: to Identify causative genes and common features of PAI.

Methodology:

- Study Design is retrospective cross-sectional study by reviewing Medical records.
- Inclusion criteria: All patients following with Pediatric Endocrinology clinics at KFSHRC during 2018 with PAI.
- Exclusion criteria: All cases of Congenital adrenal hyperplasia and Autoimmune Polyglandular disease were excluded.
- IRB approved the research with RAC Number: (2181 257).
- Data were collected and entered by using Excel Sheet then analyzed by SPSS.

Result and Discussion:

- The most common causes of PAI are Adrenoleukodystrophy then Familial Glucocorticoid Deficiency and Adrenal Hyperplasia which is different from Hsieh and White study⁴.
- X-lined diseases account for 56% of them which explains predominance of male on the study.
- Adrenoleukodystrophy is common on our hospital due to availability of transplant and screening of other family members which is recommended⁵.
- ACTH resistance and adrenal hypoplasia present early on life but Majority present late.
- Different gene mutation have been identified including (ABCD1, PDE8B, NNT, NRB01, MCR, SPGL1, CDKn1c and PIK3CD).
- hyperpigmentation is most common presenting feature followed by vomiting with lethargy and family history.

Conclusion:

- Causes other than CAH should be suspected during evaluation of primary adrenal insufficiency.
- Whole exome sequencing helped in diagnosing majority of cases.

- More researches are needed to identify common genes in our society for developing Primary Adrenal Insufficiency panel.
- All male patients presenting with PAI to be screened for Adrenoleukodystrophy (VLCFFA) and adrenal hypoplasia (CK, Lipid, US, DA \bar{X} 1 gene). Also, Karyotyping is recommended for female patients.
- Consider screening all patients with PAI for proteinuria to R/o Nephrotic syndrome type 14.

P2-16

A Case of Infantile Cushing's Syndrome from McCune Albright Syndrome: The Importance of Multiple-Site Sampling for Genetic Testing

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Case Description: We report a case of a 7-month old Vietnamese boy who presented with failure to thrive and a Cushingoid appearance from 1 month old. There was no history of exogenous steroid use. On examination, height and weight were <3rd centile. He was Cushingoid with motor development delay. There were multiple large café-au-lait lesions over the sacral region but no limb asymmetry to suggest fibrous dysplasia.

Endocrine investigations were consistent with adrenal Cushing's syndrome: 8am serum cortisol 852nmol/L (normal range, NR 123.0-626.0), ACTH 2.1pg/mL (NR 7.2-63.3), failure of cortisol suppression with the overnight dexamethasone suppression and low dose dexamethasone suppression tests. In addition, serum testosterone was elevated at 3.85nmol/L (NR 0.42-0.72) as was DHEA-S at 26umol/L (NR 0-1.2). Adrenal CT did not reveal any gross masses. There were no liver or cardiac comorbidities. DNA extraction from peripheral blood and skin swab returned negative, but repeat testing on buccal swab revealed a pathogenic GNAS mutation: c.601C>T(p.Arg201Cys), confirming the diagnosis of McCune Albright syndrome (MAS). Both parents were negative for the mutation.

Our patient was given a test dose of oral ketoconazole (4mg/kg/day) but developed hepatotoxicity after 1 week, making this unsuitable for therapy. Despite that, the patient improved clinically with good weight gain and linear growth, with decreasing cortisol levels to 478nmol/L within 3 months even without therapy. He was commenced on oral metyrapone 10mg/kg/day for further cortisol suppression. Within 1 week of treatment, 8am serum cortisol had normalized. Metyrapone dose was weaned step-wise until a low dose of 2mg/kg/dose, where serum cortisol remained normal throughout. He tolerated the metyrapone well with no side effects.

Discussion: Infantile Cushing's syndrome (ICS) is a rare but early manifestation of MAS, and may precede the appearance of its skin and bone manifestation. ICS is unique among MAS-related endocrinopathies in its tendency to spontaneously resolve in some cases, due to foetal adrenal regression. In our case, the spontaneous improvement seen before treatment initiation was likely explained by this phenomenon. Despite complete resolution of Cushing's

syndrome, patients will require monitoring for neurocognitive development and development of fibrous dysplasia or other endocrinopathies associated with MAS.

This case reinforces the genetic pathogenesis of MAS, which is a mosaic disease arising from post-zygotic somatic mutations of the GNAS gene and may have low mutation abundance. As such, DNA sampling from multiple sites, particularly from affected tissues, is recommended to increase the genetic diagnostic yield.

P2-17

Duodenal web presenting as pseudohypoaldosteronism in infancy

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Case Report: A 5-month-old girl born to first-cousin parents was referred to endocrinology for evaluation following two hospitalizations for vomiting and dehydration with severe hyponatremia and hyperkalemia. She had a history of recurrent emesis and poor weight gain, with a reportedly normal abdominal and renal ultrasound.

Initial evaluation showed hyponatremia with elevated renin 170 ng/ml/hr (normal 2-37 ng/ml/hr) and aldosterone 275 ng/dl (normal 5-90 ng/dl). The suspected diagnosis was pseudohypoaldosteronism type 1 (PHA). Treatment was initiated with sodium supplementation and she subsequently maintained normal sodium and potassium levels with relative improvement in weight gain and less frequent emesis.

Three months' later, she re-presented with severe bilious emesis. Abdominal X-ray indicated obstruction. Urgent ultrasound showed grossly distended, fluid-filled hyper peristaltic stomach and duodenum, indicating obstruction distal to the third part of the duodenum. An upper-GI fluoroscopic study revealed distension of the duodenal bulb and descending loop. The third part of the duodenum showed funnel-shaped narrowing and obstruction to the flow of contrast. These findings suggested a duodenal web or duodenal stenosis/partial atresia. At laparotomy, a duodenal web was found and the patient underwent duodenoejunostomy.

Following surgical correction, the patient had complete resolution of emesis with normalization of the electrolytes, renin and aldosterone. She no longer required sodium supplementation. Genetic testing for PHA was negative.

Conclusion: This rare case highlights the presentation of transient PHA secondary to intestinal obstruction. Only one similar case has been previously described in an infant¹. Urinary tract infection or obstruction are the most commonly found causes of **secondary transient PHA in infancy**. In the scenario we describe, PHA is due to gastrointestinal losses of sodium and water resulting in decreased renal perfusion from dehydration and consequent rise in renin and aldosterone. This gives the biochemical picture of PHA.

¹ Nissen M, Dettmer P, Thränhardt R, Winter K, Niemeyer T, Tröbs RB. Congenital Jejunal Membrane Causing Transient Pseudohypoaldosteronism and Hypoprothrombinemia in a 7-Week-Old Infant. *Klin Padiatr*. 2017 Sep;229(5):302-303.

P2-18**A rare case of pseudohypoaldosteronism in a neonate secondary to congenital hydrometrocolpos**

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Background: Hydrometrocolpos is a condition resulting in distension of the vagina and uterus due to accumulation of secretions (other than blood), caused by increased oestrogenic stimulation and vaginal outflow obstruction. The incidence in term neonates is 0.00014-0.001%. The condition presents at extremes of childhood, at birth when maternal circulating hormones are raised and at menarche when oestrogen production commences. Pseudohypoaldosteronism (PHA) due to obstructive uropathy, urinary tract infections and congenital urogenital malformations have been reported in the literature, however, there are no reports of PHA associated with hydrometrocolpos due to a common urogenital tract.

Case Report: A female baby, preterm at 35 weeks gestation, birthweight of 2100g was noted to have an abdominal mass soon after birth. Ultrasound scan showed a round, central abdomino-pelvic cystic mass with bilateral renal major pelvic-calyceal dilatation and hydronephrosis. An MRI demonstrated huge distension of the vagina and uterus with compression of adjoining structures consistent with hydrometrocolpos. Cysto-vaginoscopy revealed a common urogenital tract. The hydrometrocolpos was drained and child later discharged home.

She subsequently re-presented at 6 weeks of age, unwell, vomiting, pale, tachycardic with poor weight gain. Her results showed a metabolic acidosis, anaemia (haemoglobin 69g/dL), hyponatraemia (sodium 117mmol/L), hyperkalaemia (potassium 7.1mmol/L) and abnormal renal function. Urine examination showed microscopic haematuria but no suggestion of infection. She was initially treated for salt losing adrenal crisis so received a 10ml/kg bolus of 0.9% sodium chloride, hydrocortisone and fludrocortisone. She also received bicarbonate, with intravenous calcium gluconate and salbutamol for treatment of hyperkalaemia, and a blood transfusion as imaging showed a re-accumulation of the mass with internal haemorrhage. After stabilisation she had cystovaginostomy and only milky fluid was drained from the mass. Further investigations demonstrated raised aldosterone and renin and cortisol, 17-hydroxyprogesterone and urinary electrolytes within the normal ranges. These results and resolution of signs following surgery demonstrate a pseudohypoaldosteronism.

Conclusion: Whilst cases of PHA due to obstructive uropathy has been described previously, our case is unique as to our knowledge, there are no reports of obstruction uropathy secondary to hydrometrocolpos secondary to a common urogenital tract. The mechanism by which PHA occurs in obstruction involves renal tubular dysfunction due to pressure from hydronephrosis and the release of intrarenal cytokines. In addition, there is an immature or resistant renal tubular responsiveness to aldosterone during infancy. This leads to a picture with high circulating aldosterone levels but hyponatraemia and hyperkalaemia. Clinicians should be aware of this uncommon presentation.

P2-19**Hyperandrogenism in a 13-year-old girl due to glucocorticoid receptor mutation**

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Glucocorticoid resistance syndrome (GRS) is a rare genetic disorder caused by inactivating mutations of the *NR3C1* gene encoding the glucocorticoid receptor. The phenotypic spectrum is broad but typically includes symptoms of adrenal insufficiency, mineralocorticoid excess and hyperandrogenism. So far, about 20 different mutations in *NR3C1* presenting with the GRS phenotype have been reported.

We report a 13-year-old girl that presented with severe hirsutism and clitoromegaly. No suppression of cortisol following short overnight dexamethasone test, repeated elevated urinary free cortisol (UFC) and elevated ACTH indicated a diagnosis of Cushing syndrome. Imaging evaluation by brain and abdominal MRI revealed normal pituitary and adrenal glands. Based on the contradiction between the phenotype, with absence of manifestations of Cushing syndrome, and the laboratory findings that indicated Cushing syndrome, GRS was suspected.

Sanger sequencing of *NR3C1* identified a previously reported heterozygous mutation, c.1759_1762dupTTAC; p.His588Leufs*5, which results in a frameshift and stop codon 5 amino acids forward, in the proband and in her father. Other family members were negative for the identified mutation. The father was asymptomatic but had elevated 24-h UFC. Treatment with a low dose of dexamethasone improved the hirsutism and her well-being, but follow-up is needed.

The reported case demonstrates the unique phenotype of GRS and highlights awareness of this rare condition. Glucocorticoid receptor sequencing is recommended in cases with discrepancies between laboratory findings that suggest Cushing syndrome and clinical manifestations of hyperandrogenism and mineralocorticoid excess with no symptoms of glucocorticoid excess.

P2-20**Polydipsia, hyponatremia and a biochemical profile of aldosterone synthase deficiency**

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Background: Aldosterone synthase deficiency (ASD) is caused by biallelic inactivating *CYP11B2* variants. Infants mainly present with failure to thrive and salt wasting in early infancy. Moreover,

different factors may cause downregulation of aldosterone synthase and secondary deficiency.

Objective and Hypotheses: We present a toddler with polyuria and polydipsia and steroid hormone precursors suggestive of ASD, but normal *CYP11B2* sequencing. We discuss differential diagnoses of ASD.

Case: A 1.5-year-old German boy was admitted with a first non-febrile status epilepticus due to hyponatremia (119 mmol/l). His previous history was uneventful. He was born at term (weight at birth 3580 g, 52 cm), did not show any problems in neonatal age or infancy, had thrived well, without vomiting, and reached developmental milestones adequately. However, parents had noted polyuria and polydipsia (at time of presentation > 2000 ml/d) since early infancy. After a short period of reduced fluid intake during intercurrent illness, he presented with marked hyponatremia of 119 mmol/l with normokalemia (4.4 mmol/l), but no signs of severe dehydration in clinical examination or blood gas analysis (pH 7.29, pCO₂ 52 mmHg, BE -2 mmol/l). With calculated infusion therapy, his status rapidly improved. Meningitis, infection and heart disease were ruled out and cerebral MRI was normal, there was no sign of SIADH. Aldosterone was detectable in hyponatremia, but inadequately low considering the context of severe hyponatremia. After normalization of sodium, an ACTH stimulation test was performed: Cortisol responded adequately and CAH was ruled out. Interestingly, corticosterone and 11-desoxycorticosterone showed an exaggerated response while aldosterone, being very low at baseline, did not show any relevant increment, suggesting a deficiency in terminal steps of aldosterone synthesis. Genetically, the diagnosis of ASD could not be confirmed. We only detected a heterozygous common variant in the coding sequence of the *CYP11B2* gene. As a differential diagnosis, besides putative intronic or regulatory mutations, other factors besides the *CYP11B2* gene may influence aldosterone production. With fludrocortisone treatment (0.1 mg/day) the boy continued to thrive, however, polydipsia remained.

Conclusion: ASD is an important differential diagnosis in isolated hyponatremia in toddlers. However, differential diagnosis can be challenging when diagnosis cannot be confirmed genetically.

P2-21

Fludrocortisone treatment in a child with Postural Orthostatic Tachycardia Syndrome (POTS): a case report

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Background: Postural orthostatic tachycardia syndrome (POTS) is a multifactorial condition, which implies symptoms as fatigue, tachycardia, sleep disorders and autonomic symptoms.

The fundamental clinical sign is the manifestation of an abnormal increase in heart rates of at least 40 bpm within 10 minutes assuming an upright position, delineating a condition of orthostatic intolerance and decreasing quality of life.

Objective: To describe a case of a debilitated boy with POTS treated with fludrocortisone, justifying our therapeutic choice based on syndrome's pathophysiology.

Case Report: An 8-year-old boy presented repeated episodes of tachycardia, pallor, periumbilical abdominal pain and frontal headache, followed by ground fall and loss of consciousness lasting a few seconds. Therefore, he performed first-level blood tests, ECG, chest X-ray, abdominal ultrasound and *fundus oculi*, resulting normal. Moreover, due to the worsening of the symptoms, he performed an echocardiography and a recording Holter pressure, without finding anomalies.

At our attention, to rule out intracranial pathology, a brain MRI and electroencephalography were made, resulting without abnormalities. Finally, a head-up tilt table test was performed, showing a vasovagal response, so the therapy with midodrine hydrochloride at the dose of 2.5mg/die was started.

After the hospitalization, his symptomatology has become more frequent. So he was admitted for second times in our Hospital, where he began to present increased vertigo in the immediate transition from supine position to standing up, with a blood pressure of 70/42mmHg and heart rate of 135bpm. He performed dosage of aldosterone, renin and catecholamines in supine position and after 10 minutes in orthostatism. Laboratory results showed normal values of catecholamines, but they indicated a paradoxical increase of renin and aldosterone values, higher in supine position, respectively 201,4microUI/ml and 21,80ng/dl. A diagnosis of POTS was made and the therapy with fludrocortisone acetate at dose of 0,05mg/die was started.

At demission our patient was good and, at first follow-up, the laboratory values did not show the paradoxical increase of renin and aldosterone.

Discussion and Conclusion: The management of POTS paediatric patients is very controversial, because of lack of trial studies. A complete clinical and diagnostic evaluation can provide the basis for a right management, based on syndrome's pathophysiology. In our case, we identified a hypovolemic form, so we expanded plasma volume with fludrocortisone, an aldosterone analogue, that increases sodium retention from the tubular fluid into the plasm. This empirical approach has allowed our patient a gradual recovery of his activities.

P2-22

An atypical case of Ectopic ACTH syndrome in an adolescent boy

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Background: Ectopic ACTH syndrome (EAS) is exceedingly rare in children and scarcely reported. Pancreatic Neuroendocrine tumours (NET) can rarely lead to secretion of ectopic adrenocorticotrophic hormone (ACTH).

Case Characteristics: A 14-year-old adolescent boy presented with isolated hyperpigmentation and intermittent abdominal pain and underwent evaluation for primary adrenal insufficiency, but turned out to have subclinical Cushing's instead. An incidental pancreatic mass discovered on routine ultrasonogram revealed the source of ACTH. He underwent successful excision with resolution of hypercortisolism. The histopathology revealed a Pancreatic Neuroendocrine Tumor (NET) and immunohistochemistry (IHC) was positive for ACTH stain.

Message: The extra-ordinary features of this case were the absence of clinical Cushing's in the presence of severe biochemical hypercortisolism, the equivocal ACTH levels not correlating with the degree of hypercortisolism or hyperpigmentation, the incidental discovery of pancreatic mass laying rest to the dilemma over source of ACTH- Pituitary versus Ectopic, and the rarity of Pancreatic NET causing EAS in children.

P2-23

Girls with idiopathic premature adrenarche achieve normal adult height

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Introduction: Studies about pubertal onset and the menarcheal age in girls with the antecedent of idiopathic premature adrenarche (IPA) are limited and with discordant results. For these reasons, we created a cohort of girls with the diagnosis of IPA. The objectives of our study were: a) to know the age of pubertal onset; b) to evaluate menarcheal age; c) to determine the growth rate in the first two years after the IPA diagnosis; d) to collect adult height data in these girls.

Material and Methods: IPA girls cohort with the following inclusion criteria: appearance of pubic and/or axillary hair before 8 years old after excluding other pathologies causing hyperandrogenism as ovarian or adrenal tumours (detected by ultrasound) and congenital adrenal hyperplasia (evaluated by ACTH stimulation test). We planned a follow-up of these patients from their diagnosis until reaching adult height, collecting anthropometric and pubertal development data through visits every six months.

Results: This cohort was composed of 81 girls with IPA, whose average age at diagnosis was 7.54 years (7.26 - 7.82). At that time, the mean difference between their bone and chronological age was 0.90 years (0.72 - 1.08). Their mean height was +1.59 SDS (1.38 - 1.80), significantly greater than the target height which was +0.30 SDS (0.09 - 0.52) ($p < 0.001$). The growth rate in the first two years after diagnosis was +1.36 SDS (0.98 - 1.75) for the first year and +1.62 SDS (1.06 - 2.18) for the second year, respectively. The mean age of progressive thelarche appearance (Tanner II stage) was 9.62 years (9.38 - 9.86), with a mean menarcheal age of 11.50 years (11.18 - 11.83). The mean of menarcheal age of their mothers

was 12.14 years (11.83 - 12.46), significantly higher ($p = 0.04$). At the time of this study, 34 girls (42% of the cohort) reached an average final height of +0.72 SDS (0.38 - 1.05), significantly higher than the predicted adult height at diagnosis [+0.24 SDS (-0.03 - 0.52), $p = 0.02$] and slightly higher, but not reporting significant differences with their target height [+0.3 SDS (0.09 - 0.52)].

Conclusions: Our cohort of girls with IPA shows advanced pubertal development compared to its mothers but this finding does not seem to affect their adult height.

P2-24

Adult height and growth pattern in patients with classic congenital adrenal hyperplasia

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Background: Congenital adrenal hyperplasia (CAH), mostly caused by 21-hydroxylase deficiency, is autosomal recessive disorder characterized by impaired cortisol synthesis. It can be presented with a combination of aldosterone and cortisol deficiency and androgen excess. Therefore, excess production of androgen and glucocorticoid replacement can result to early bone maturation and ultimately diminished adult height (AH).

Objectives: The purpose of this study was to obtain objective data on AH with classic CAH patients and analyze the affecting factors on AH. Also we evaluated growth pattern during age increase.

Study Design: We retrospectively reviewed the longitudinal medical records of 40 children with classic CAH (male [n=19]: 9 salt-wasting (SW), 10 simple-virilizing (SV); female [n=21]: 8 SW, 13 SV) who reached AH at Pediatric endocrinology clinic of Severance hospital from 1977 to 2015. We also analyzed the affecting factors on AH, and assessed growth patterns with serial height standard deviation score (SDS) dividing into following stages of growth: early childhood (0-4.99 years), mid-childhood (5-9.99 years), and adolescence (10-15 years)

Results: AH (162.7 ± 9.72 cm) was significantly shorter than the midparental height (MPH) (172.5 ± 3.40 cm) in male patients ($P < 0.001$), and similarly, AH (154.5 ± 6.45 cm) was significantly shorter than the MPH (158.7 ± 2.96 cm) in female patients ($P = 0.002$). Accordingly, the AH SDS was meaningfully lower than the MPH SDS in both sex (males: $P < 0.001$, females: $P = 0.002$). Considering subtypes, SV had tendency to attain shorter AH than SW. In addition, the affecting factors on AH were analyzed that they were not significantly associated with subtype, age at diagnosis, dose of steroid, except MPH. Height SDS for chronologic age showed gradual decrement during childhood to adolescence (males: 0.5 ± 2.51 at early childhood, 0.8 ± 2.26 at mid-childhood, 0.2 ± 1.62 at adolescence; females: -0.4 ± 1.40 , -0.2 ± 2.01 , -0.3 ± 1.42 at those same periods). The final AH SDS was -1.6 ± 1.98 in males and -0.81 ± 1.45 in females.

Conclusion: Reduced AH was observed in children with classic CAH compared with their given parental height, regardless of sex and subtype. Furthermore, the height SDS tended to decrease in accordance with age increase, so this finding suggests that proper intervention about growth assessment is needed in children with CAH.

P2-25

Cushing Syndrome due to an adrenacortical carcinoma in a baby with atypical Beckwith-Wiedemann Syndrome

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Beckwith-Wiedemann syndrome (BWS) is a congenital tumor-predisposition syndrome of which around 70% develops because of the methylation defects in the imprinted genes at chromosome 11p15.5. *KCNQ1OT1* hypomethylation is the most common underlying genetic aberration in sporadic the BWS, accounting for 50% of the sporadic cases but confers the least tumor risk. We present a 5 month-old girl who presented with an excessive weight gain, cushingoid face, arrested growth in height and head circumference since 2 months of age. She was born following an in vitro fertilization (IVF) pregnancy to non-consanguineous parents with negative familial history for malignancies. She had signs of Cushing syndrome, nevus flammeus between eyebrows, microcephaly, a palpable mass on upper right abdomen and Tanner stage 2 pubarche at physical examination. Her biochemical, imaging and immunohistochemical established the diagnosis of adrenocortical carcinoma as a cause of Cushing syndrome. There was no adrenal cortex cytomegaly at histopathological evaluation. Methylation analysis of the imprinted domains at chromosome 11p15.5 revealed hypomethylation at KvDMR(*KCNQ1OT1* gene). Except for a nevus flammeus and adrenocortical carcinoma, she had no features of the BWS. Growth rate of height and head circumference has turned to normal after tumor resection. This case establishes that *KCNQ1OT1* hypomethylation should not only be considered in cases with a clear BWS phenotype but in all pediatric cases of apparently sporadic adrenocortical carcinoma.

Bone, Growth Plate and Mineral Metabolism

P2-26

Successful Parathyroidectomy with Intraoperative Parathyroid Hormone Monitoring in a Neonate with Severe Primary Hyperparathyroidism due to a Novel CASR Mutation

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Neonatal severe primary hyperparathyroidism (NSHPT) is a rare and life-threatening disorder caused by inactivating mutation in *CASR* gene, which encodes Ca-sensing receptor. NSHPT leads to severe neonatal hypercalcemia with inappropriately increased serum intact parathyroid hormone (iPTH) and decreased urinary Ca excretion. Hydration, forced diuresis, calcitonin, bisphosphonates and cinacalcet have been used to lower serum Ca prior to surgery. Total parathyroidectomy is the standard treatment but is challenging in neonatal period. We present a female infant who was born to consanguineous parents and presented at the age of 7 days with lethargy and respiratory distress. Chest radiograph revealed bell-shaped thoracic cage, multiple rib fractures and generalized osteopenia. Blood chemistries showed markedly elevated serum Ca at 24.8 mg/dL, P 2.1 mg/dL and iPTH 872 pg/mL. The fractional excretion of urinary Ca was relatively low at 2.6%. Severe neonatal hypercalcemia with findings of serum P, iPTH and urinary Ca levels led to the diagnosis of NSHPT. She was promptly treated with intravenous saline, furosemide, salmon calcitonin and bisphosphonates. However, serum Ca remained elevated at 11-15 mg/dL. Cinacalcet was then initiated with a maximum dose of 90 mg/m²/day without success. Therefore, total parathyroidectomy was undertaken at 2 months of age. Owing to the difficulty of performing parathyroidectomy in a small infant, intraoperative iPTH levels were monitored to ensure complete removal of parathyroid glands. The serum iPTH fell from the preoperative level of 755 to 26 pg/mL at 20 minutes after excision of 4 parathyroid glands. She developed hypocalcemia secondary to hypoparathyroidism 10 days after the operation. *CASR* mutation analysis identified a novel homozygous nonsense mutation, c.1660C>T (p.Arg554*). The mutation leads to a stop codon and is predicted to produce a shorter protein from 1088 to 554 amino acids. Her parents were cousins and had slightly elevated serum Ca and iPTH but low urinary Ca excretion. Each parent is likely to have the heterozygous mutation. However, the familial mutation test has not been performed. Our findings demonstrated a novel p.Arg554* mutation as a cause of NSHPT which did not respond to the medications including cinacalcet. A mutation analysis could minimize an unnecessary prolonged period of medications.

P2-27

The First Case Report of SEMD-JL1 in China

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Background: Spondyloepimetaphyseal dysplasia with joint laxity type 1(SEMD-JL1) is a rare entity with a recessive inheritance. It is one of the genetic skeletal disorders (GSD) and *B3GALT6* loss-of-function mutations were found in individuals with SEMD-JL1 from several families. However, there was no case described in China.

Case Report: An 8-year-old boy presented to our hospital with short stature, hyperlaxity with secondary spinal malalignment, ulnar subluxation and craniofacial alterations. The amplified DNA was captured with a disease related Gene Panel using biotinylated oligo-probes (MyGenostics GenCap Enrichment technologies). Molecular analyses did not show any other mutation but compound heterozygous variants in the *B3GALT6* gene (c.694C>T and c.539_540insCCT), inherited from his parents. Then this boy was diagnosed SEMD-JL1. This is the first case report of SEMD-JL1 in China. While the c.539_540insCCT compound heterozygous mutation in *B3GALT6* gene is not described before.

Conclusion: SEMD-JL1 is caused by homozygous or compound heterozygous mutations in the *B3GALT6* gene. We recommend that all the patients who have the clinical manifestations of GSD should undergo genetic analysis. This will be important for understanding the genetic laws of such diseases.

P2-28

Clinical radiographic and biochemical findings of three patients with hypophosphatasia carrying the same mutation

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Background: Hypophosphatasia (HP) is a rare inherited disorder characterized by defective bone and tooth mineralization and caused by deficiency in the tissue non-specific alkaline phosphatase gene (ALPL). The symptoms are remarkably variable in their clinical expression, and relate to numerous mutations in this gene.

Aim: The purpose of this study was to document the clinical, biochemical and radiologic aspects of the three relative patients (two sibling and their one cousin) with childhood hypophosphatasia carrying the same mutation gene.

Methods: Clinical and radiographic examinations were carried out. We collected medical and dental history in the kindred and biochemical data. Finally, mutations in the ALPL gene were tested by DNA sequencing.

Results: Low levels of alkaline phosphatase (ALP) in serum and phosphoethanolamine (PEA) in the urine were found. Affected our patients have a history of delayed walking. Bone pain (due to

stress fractures) and joint pain (due to deposition of calcium pyrophosphate dihydrate) were a frequent symptom in the our patients. Characteristic dental symptoms were premature deciduous teeth loss, premature exfoliation of fully rooted primary teeth, severe dental caries, root resorbsion and alveolar bone loss. Clinical and radiologic examinations revealed delayed eruption of permanent teeth and large pulp chambers of all first permanent molars.

Conclusion: Even in two sibling and cousin who share the same mutations, there may be significant differences in the HPP table and severity. A good co-operation between pediatrician and dentist is need for a better management of the patients. The dentist plays a critical role in the detection and early diagnosis of the disease.

P2-29

Clinical and Genetic Characteristics of Pseudohypoparathyroidism Type 1A in Children Based on Single-center Cohort Study

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Background: Pseudohypoparathyroidism 1A (PHP1A) is a rare disease caused by mutations of *GNAS* gene, and characterized by Albright's hereditary osteodystrophy (AHO) and resistance to multiple hormones. Infantile onset is often missing diagnosed due to atypical clinical manifestations. This study aims to summarize the clinical and genetic characteristics of child onset PHP1A patients.

Methods: 12 patients were diagnosed as PHP1A in our hospital from 2013 to 2019 based on the genetic and clinical characteristics. Sanger sequencing and methylation-specific multiple ligation-dependent probe amplification (MS-MLPA) were used for genetic diagnosis. Anthropological parameters, laboratory and imaging findings were collected for clinical diagnosis.

Results: The average onset and diagnose age was 6.4y (0.2-12.1y) and 8.1y (0.2-12.2y), respectively. *GNAS* mutation was detected in 3 of the 12 patients including c.568_571delGACT, c.521_524delACTG and c.939delT, and patient B with a family history of PHP. 6 of the remaining 9 mutation negative were confirmed with methylation abnormalities, and the other 3 patients refused to do MS-MLPA analysis. Recurrent tetany is the most common symptoms and reason for visiting the doctor (8/12, 66.7%), following with growth retardation (2/12, 16.7%), subcutaneous nodules (1/12, 8.3%), epilepsy(1/12, 8.3%). All the patients present with different kinds of AHO features, 4 short stature, 4 brachydactyly, 3 mild mental retardation, 3 intracranial calcification, 2 obesity, 1 subcutaneous calcification, 1 kidney crystallization. 10 of them present with hypocalcaemia, hyperphosphatemia and PTH resistance, 3 patients with TSH resistance, 1 patient with GH deficiency. Routine calcium was prescript to all the patients. Calcitriol were also supplemented except the 2 patients with normal serum calcium, phosphorus, and PTH, who are diagnosed before 1 years old. Levothyroxine was supplemented in the patients with TSH resistance, and 1 patient also received antiepileptic therapy.

Conclusion: This study summarizes the clinical and genetic features of the child onset PHP1A. Clinical characteristics of early onset PHP1A patients, especially infants were atypical, close following up combined with gene sequencing and/or MS-MLPA analysis can help early diagnosis of PHP1A.

P2-30

A rare case of neonatal hypocalciuric hypercalcemia complicated with arrhythmia

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Background: Familial hypocalciuric hypercalcemia is a rare, lifelong, but benign hereditary disorder due to its mild, often asymptomatic phenotype. Here we present a rare case of neonatal hypocalciuric hypercalcemia complicated with arrhythmia.

Case: A healthy male infant weighing 2636g was delivered by spontaneous vaginal delivery at term. The pregnancy had progressed normally, but neonatal arrhythmia was found by physical examination after birth. Electrocardiography demonstrated isolated supraventricular premature contraction. The baby was well so that he was discharged on day 6 with further follow-up appointment at clinic. However, on day 10, he suffered from fever due to viral infection. Biochemistry investigations revealed markedly elevated serum levels of total calcium (Ca; 12.3 mg/dL; reference range: 8.8 – 10.1 mg/dL), and alkaline phosphatase (ALP 1863 U/L; reference range: 106 – 322 U/L). Serum concentration of phosphorus was normal (4.3 mg/dL; reference range: 2.7 – 4.6 mg/dL). Physical examination revealed no particular sign of hypercalcemia. Additional laboratory tests showed elevated intact PTH (88 ng/dL; reference range: 10 – 65 pg/mL) and low renal calcium excretion (24-hour FECA < 1%). TSH and fT4 levels were slightly elevated (TSH 10.72 µIU/mL; reference range: 0.5 – 5.0 µIU/mL, fT4 2.02 ng/dL; reference range: 0.9 – 1.7 ng/dL) with no physical sign of hypothyroidism. Ultrasonography of the neck was performed which revealed no evidence of parathyroid adenoma. He was diagnosed with hypocalciuric hypercalcemia, although the family history of hypercalcemia was unremarkable. He was well on day 24 and the total calcium levels had been maintained at same levels without any treatment. Genetic sequencing of calcium sensing receptor gene mutation is under investigation.

Conclusion: Previous reports have shown that hypercalcemia in patients with primary hyperparathyroidism increased the occurrence of arrhythmia such as supraventricular premature contractions. Therefore, clinicians should consider electrolyte abnormalities including hypercalcemia in the differential diagnosis of neonatal arrhythmia.

P2-31

Experience of burosumab therapy in four children with X-linked hypophosphataemia in Saudi Arabia

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X-linked hypophosphataemia (XLH) is the most common form of inherited hypophosphataemic rickets, caused by loss-of-function mutations in the gene encoding phosphate-regulating endopeptidase homologue X-linked (PHEX), resulting in excess circulating fibroblast growth factor 23 (FGF-23).^{1,2} In children, clinical features include delayed walking, waddling gait, leg bowing, pain, spontaneous dental abscesses and growth failure. Current therapies do not treat the underlying cause of the disease,² resulting in persistence of rickets, growth impairment, and gastrointestinal side effects.³ Burosumab is a novel, fully human anti-FGF-23 immunoglobulin G1 monoclonal antibody that binds and inhibits FGF-23 activity.^{4,5} Here, we describe the clinical and biochemical features of XLH in four paediatric patients treated with burosumab.

Patients (one male, three females) were aged 2–11.5 years at diagnosis. Physical symptoms included leg bowing in all patients; three patients had dental caries, two patients presented with a larger head circumference (\geq 95th percentile), and one patient had craniosynostosis. Other physical symptoms included short stature and wide wrists. Baseline biochemical investigations revealed low phosphate (PO_4) levels in all patients (0.85–0.90 mmol/L), elevated parathyroid hormone (PTH) levels of 3.07–16.06 pmol/L, high alkaline phosphatase (ALP) levels of 376–937 U/L and low renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) of 0.61–0.81. Intact FGF-23 levels ranged from 77 to 139 RU/mL, with highly elevated levels in three patients. Genetic testing confirmed PHEX mutation in all patients. Despite receiving PO_4 supplementation and a vitamin D analogue (alfacalcidiol), clinical signs of rickets did not improve, therefore burosumab was considered. Prior therapies were stopped 1 week before treatment initiation with burosumab (s.c.) and serum PO_4 was measured every 2 weeks for the first month, monthly for 2 months and then every 3 months as appropriate after injection.

Burosumab treatment increased PO_4 levels in all patients after the first injection and after 3 months, all patients had levels within the reference range (1–1.95 mmol/L). Mean serum ALP levels decreased from baseline in all patients after 3 months of treatment, and PTH levels were stable throughout the treatment period. TmP/GFR increased from baseline in all patients after 3 months of burosumab treatment (increase of 0.17–0.51).

In four paediatric cases of XLH, burosumab treatment increased serum PO_4 , decreased mean serum ALP, and improved TmP/GFR. No adverse effects were observed. These cases confirm previous findings³ that burosumab is effective in treating paediatric patients in whom conventional therapy had limited success.

P2-32**Pediatric patients with heterozygous ALPL mutation show a broad clinical phenotype**

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Introduction: Hypophosphatasia (HPP) is a congenital disorder of the bone and mineral metabolism. It is based on mutations in the ALPL gene, which codes for tissue-unspecific alkaline phosphatase (TNSAP).

Methods: The casuistic of 3 children with heterozygous ALPL mutation are presented. The patients were identified by laboratory data screening for reduced AP activity at the Children's Hospital of the University Hospital Freiburg.

Case Reports: Patient 1: 11-year-old boy with family dwarfism. Dental problems on the father's side are known. The boy had no complaints at the time of the study. The activity of alkaline phosphatase was reduced (AP 126 IU/l [152-369]), pyridoxal phosphate (PLP) was clearly elevated ($> 100 \mu\text{g/l}$, note: intake of vitamin preparation with vitamin B6) and phosphoethanolamine (PEA) in the urine was borderline increased ($14.4 \mu\text{mol/l}$). The mutation analysis revealed a heterozygous mutation in the ALPL gene (c.145[T>G]; [T=]), which has a function-reducing effect on the protein.

Patient 2: 12-year-old boy without positive family history for HPP-specific symptoms and without symptoms at the time of the study. The activity of alkaline phosphatase was slightly decreased (AP 139 IU/l [159-405]), PLP was increased ($62 \mu\text{g/l}$) and PEA in urine was also increased ($23.8 \mu\text{mol/l}$). The mutation analysis revealed a heterozygous mutation in the ALPL gene (c.1204delC;[C=]), which had a diminishing effect.

Patient 3: 13-year-old girl with chronic pain syndrome. The family anamnesis is bland. The patient suffers from recurrent severe muscular-skeletal pain and abdominal pain. The activity of alkaline phosphatase was slightly decreased (AP 80 IU/L [104-385]), PLP was significantly increased ($> 100 \mu\text{g/l}$) and PEA in urine was marginally increased ($14.4 \mu\text{mol/l}$). The mutation analysis revealed a heterozygous mutation in the ALPL gene (c.147[G>A]; [G=]), which has a function-reducing effect on the protein.

Conclusion: Children with heterozygous ALPL mutation show suggestive laboratory findings with reduced alkaline phosphatase activity and increased concentrations of substrates PLP and PEA. The clinical phenotype is highly variable, from asymptomatic carrier status to clinical manifestations with small stature or chronic muscular-skeletal pain. The indication for enzyme replacement therapy should be decided individually.

P2-33**Growth and Bone Mineral Density in Egyptian Children with Congenital Adrenal Hyperplasia on Glucocorticoid Replacement Therapy; A Single Center Study**

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Background: Children with congenital adrenal hyperplasia (CAH) need chronic glucocorticoid therapy, both to replace congenital deficit in cortisol synthesis and to suppress the overproduction of androgens by the adrenal cortex. High doses of glucocorticoid taken chronically might affect bone metabolism and lead to alterations of bone mass in this condition. In particular, they could increase bone resorption rate. Bone mineral density (BMD) by energy X-ray absorptiometry (DEXA) scan is a very strong predictor of bone strength and biochemical markers of bone formation and turnover have been developed to look at bone metabolism.

Aim: The aim of the present work was to assess the effect of glucocorticoid replacement therapy (hydrocortisone or prednisone) in children with CAH on growth and bone mineral density.

Subjects: The present study was conducted on 60 children (2 groups): Group 1 included 30 children, diagnosed with congenital adrenal hyperplasia attending the Endocrinology Clinic in Alexandria University Children's Hospital. Group 2 included 30 healthy children matching in age and sex as controls.

Methods: Careful history taking and thorough clinical examination stressing on anthropometric measurements. Pubertal status was assessed by Tanner staging. Laboratory investigations as calcium profile (corrected calcium for albumin, serum phosphorus, and alkaline phosphatase function), serum 17-OH progesterone and serum osteocalcin level were done. BMD was done by dual-energy X-ray absorptiometry (DEXA scan) of the lumbar spine.

Results: Serum osteocalcin level it was significantly lower in the patient's group (50.28 ng/ml) than in the controls group (80.53 ng/ml) with P value <0.001 . (Table 6). Twenty patients (66.7%) were found to have normal BMD (Z score $> -1 \text{ SD}$) while 6 patients (20%) were found to have osteoporosis (Z score $<-2 \text{ SD}$) and 4 patients (13.3%) had osteopenia (Z score from -1 to -2 SD). 22 patients (73.3%) were treated by prednisone and 8 patients (26.7%) were treated by hydrocortisone. There was no significant difference in growth, biochemical parameters and BMD between children receiving prednisone and children receiving hydrocortisone. BMD had significant positive correlation with serum osteocalcin level ($r=0.475$, $p=0.008$) and negative correlation with both alkaline phosphatase level ($r=-0.460$, $p=0.011$) and serum 17OH progesterone ($r=-0.376$, $p=0.040$).

Conclusion: Children with CAH may have reduced BMD and increase bone turnover compared with controls.

P2-34

Chronic Bone Disease in Pediatric Sickle Cell Disease Including a Case of Successful Bisphosphonate Therapy

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Background: Avascular necrosis (AVN) is common in Sickle Cell Disease (SCD), frequently involving the femoral and humeral head and less commonly involving the spine. AVN leads to joint collapse, chronic pain and disability, and often requires joint replacement in early adulthood. There are no medical therapies for AVN in SCD despite the high burden of disease and there are no published reports of bisphosphonate therapy in this condition.

Methods: We performed a retrospective review of our centre's cohort, looking at bone disease in pediatric patients with sickle cell disease.

Results: In our tertiary care centre, we have a pediatric cohort of 97 patients with sickle cell disease. Of these, 57% were male; age at youngest presentation was 2 years old; 86% are HgSS, 15% have bone abnormalities including AVN of the femur, humerus, and vertebral bodies. We had rare bone diseases including orbital hematoma, subgaleal hematoma, lytic and sclerotic lesions of the femur and pelvis, and vaso occlusive crisis of the jaw resulting in facial neuropathy. We highlight the radiographic findings and a case of successful bisphosphonate therapy.

Successful Case of Bisphosphonate Therapy: An adolescent male with HbSS had spontaneous orbital hematoma and significant bone comorbidity including AVN of the humerus and femur. He had chronic back pain and recurrent vaso occlusive crises localized to the lumbar region. Spine XRay and MRI demonstrated avascular necrosis of multiple vertebral body involvement and significant loss of vertebral height. The patient was treated with intravenous bisphosphonate. He reported decreased pain and imaging of the vertebral bodies showed stabilization of vertebral bodies without additional deterioration.

Conclusion: Sickle Cell AVN develops in childhood and may affect the femur, humerus and spine, and joint involvement is often bilateral. In children with SCD and chronic back pain or vaso-occlusive crises localized to the back, consider avascular necrosis of the spine. There may be a role of intravenous bisphosphonates in arresting the progression of AVN in children with sickle cell disease.

Table 1. Summary of bone disease in a tertiary cohort

N =14 (%)	Type of bone disease
9 (64%)	Vertebral avascular necrosis including H shaped vertebral bodies, wedged vertebral bodies, and end-plate irregularity
1 (7%)	Humeral AVN (unilateral)
4 (29%)	Femoral head AVN (all cases were bilateral)
5 (36%)	Other: lytic sclerotic lesions of the femurs and pelvis, orbital hematoma, subgaleal bleed, vaso occlusive crisis of the jaw causing neuropathy Radiologic findings will be presented visually

P2-35

Clinical and genetic characteristics of 168 Russian patients with hypophosphatemic rickets

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Background: Hypophosphatemic rickets (HR) comprises a group of inherited forms of rickets characterised by renal phosphate wasting. Taking info account the latest advances in HR therapy, it now becomes of interest to better define the mutational and phenotypic spectra of disease.

Objective and Hypotheses. The aim of this study was to clinically characterize and perform genetic analysis of 168 cases with HR.

Method. 168 patients (aged from 1 month to 56 years; female, n=111; male, n=57) with clinical and radiological sings of rickets, low serum phosphate and low tubular reabsorption of phosphate were included in the study. There were 52 familial and 116 sporadic cases from 137 families. The method of Thacher was used to evaluate a Rickets Severity Score (RSS). 'Rickets panel' genes were sequenced using a custom Ion Ampliseq gene panel and PGM semiconductor sequencer (Ion Torrent). Bioinformatic analysis was performed using Torrent Suite (Ion Torrent) and ANNOVAR (annovar.openbioinformatics.org) software packages.

Results: The mean age at diagnosis was 7.5 years (aged from 2 month to 17 years). Clinical symptoms of HR included deformities of leg bones (90%), muscle weakness (75%), multiple dental abscesses (72%). The mean height SDS was -2.34 ± 1.8 , with 62.7% of patients less than -2 SD (n=144). 10 children that were diagnosed with HR and started treatment before the age of 2 had mean height SDS= -1.2 ± 0.3 and mild leg deformities. The mean RSS was 4.5 points (range 1.5–10) (n=25). Mutations were identified in 92.3% of familial and 84.4% of sporadic cases. In 143 probands mutations were detected in *PHEX*, 70 of which were novel. Mutations were also detected in other genes: *FGF23* (n=1), *SLC34A3* (n=1) and *CLCN5* (n=1).

Conclusion: This study showed the predominance of *PHEX* mutations among the patients with HR in Russia. We identified 117 *PHEX* mutations, including 70 unreported ones. Earlier diagnostic and treatment can result in less severe complications and improve the quality of life of patients with HR.

A 10-year-old girl with primary hypoparathyroidism and systemic lupus erythematosus (SLE)

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Introduction: Parathyroid Hormone (PTH) is one of the principal regulatory hormones for calcium and phosphate homeostasis. Reduced PTH concentration in hypoparathyroidism is characterised by hypocalcaemia and hyperphosphataemia.

Case Presentation: We report a ten-year-old girl who was admitted to the Department of Paediatrics, Endocrinology, Diabetology with Cardiology due to repeated seizures, hypoalcaemia with suspected hypoparathyroidism. Her postnatal medical history was unrevealing, and there was no history of candidiasis. Regarding family history, patient's mother reported epilepsy and arrhythmias. The girl was admitted severely unwell. Physical examination revealed a non-specific rash on the whole body surface (probably an allergic reaction to oxcarbazepine). Because of the low PTH concentration (<3pg/ml; NR 10-60) and typical biochemistry (total serum calcium concentration 0.8 mmol/l, plasma phosphate 4.1 mmol/L), primary hypoparathyroidism was confirmed. Other hormonal analyses showed no thyroid or adrenal disorders. Ultrasonography of the thyroid and parathyroids showed a hyperechoic area in the thyroid left lobe (II according to Bethesda), but no parathyroid pathology. Long QTc (over 0.5 seconds) was present in the ECG. Hypocalcaemia was initially treated with intravenous and oral calcium, vitamin D₃ and vitamin D analogue i.e. alfacalcidol. Sevelamer was used for the management of hyperphosphataemia. The patient was also treated with valproic acid for the concomitant epilepsy and beta-blocker for LQTc syndrome. Calcium in the serum remained below the normal reference range, and phosphate level increased initially despite the treatment. During hospitalization the girl twice developed intermittent fever, accompanied by an elevated CRP and radiological features of pneumonia and pericardial effusion. Despite negative blood cultures and no serological evidence of viral infections she was treated empirically with antibiotics. The CT scan, MRI and PET MRI did not reveal any abnormalities. Bone mineral density measured with DXA was within the normal range. Based on the presence of standard clinical criteria, systemic lupus erythematosus (SLE) was diagnosed and the treatment with glucocorticoids was initiated, which improved parameters of calcium-phosphate balance. Further immunological

examinations revealed INF-omega antibodies before implementation of steroid therapy, with negative IL-22, IL-17A, IL-17F, IFN-lambda, IFN-omega, IFN-alpha2A, and CaSR antibodies after this treatment. Genetic diagnosis excluded AIRE and CaSR mutations.

Conclusions: Coexistence of hypoparathyroidism with SLE, the presence of INF-omega autoantibodies and normalization of calcium and phosphate serum concentration following glucocorticoid treatment may suggest an autoimmune background of the disease in the patient. However, further investigation is needed to detect specific underlying mechanism responsible for insufficient PTH secretion.

An unusual case of hyperparathyroidism: familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) associated with mutations in CLDN19

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Background: FHHNC is an autosomal recessive disorder caused by mutations in either claudin 19 or claudin 16. This is a rare disorder of magnesium metabolism with fewer than 400 reported cases throughout the literature. It is also a somewhat under-diagnosed disorder, not being commonly observed.

Case Presentation: Patient was a 2 years old female who was incidentally noted to have nephrocalcinosis as part of evaluation for urinary tract infection. Her initial workup by renal service revealed elevated PTH, hence prompting a referral to endocrine.

Laboratory work-up: 25-OH vitamin D 37ng/ml (ref 30-100ng/ml), 1,25-OH vitamin D 57ng/ml (ref 31 – 87ng/ml), Alkaline phosphatase 215 U/L (ref 129 - 291 U/L), PTH 128 pg/ml (ref 9-59 pg/ml), Calcium 10.2 mg/dL (8.9 – 10.4mg/dL), Phosphorus 4.3mg/dL (3.1 – 6.3), Magnesium 1.6mg/dL (ref 1.5 – 2.4). Urine Calcium/Cr 0.6. Her PTH level remained elevated for her calcium level on multiple repeats. A Parathyroid scan did not reveal any adenoma or nodule. On one of follow-up labs, patient was noted to have hypomagnesemia (1.4mg/dL).

Additionally, at 4 years of age, patient started to have vision problem. This prompted an ophthalmology evaluation that showed macular scarring. At this time, a suspicion of FHHNC was raised and genetic testing subsequently confirmed a C59G mutation in CLDN 19.

Patient has been on thiazide and also on magnesium supplement since diagnosis.

Literature Review: The product of CLDN19 belongs to the claudin family. It plays a major role in tight junction-specific obliteration of the intercellular space, through calcium-independent cell-adhesion activity. Defects in CLDN19 are the cause of hypomagnesemia renal with ocular involvement. This is a progressive renal disease characterized by primary renal magnesium wasting with hypomagnesemia, hypercalciuria and nephrocalcinosis associated with severe ocular abnormalities such as bilateral chorioretinal scars, macular colobomata, significant myopia and nystagmus.

There is no known cure, and treatment is largely supportive with thiazide diuretics and magnesium supplementation, although whether this helps to slow the rate of progression to end-stage renal disease is not clear at present.

Conclusion: FHHNC is a rare disorder of magnesium metabolism and often underdiagnosed. In particular, magnesium levels are often not checked and there is a spectrum of FHHNC in which the magnesium could be normal. FHHNC is a progressive disease in both renal and eyes however, the clinical course is not completely clear. Multidisciplinary approach is helpful in monitoring and management of this disease.

P2-38

Skeletal Maturity and Growth in children with Type 1 diabetes

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Background: Type 1 diabetes (T1D) being a chronic disease is likely to affect growth in children. Bone age helps in assessing the growth of child in relation to their skeletal maturity. Skeletal maturity is delayed in chronic systemic illness.

Objective: To study growth in relation to bone age and chronological age in children with T1D.

Methods: Study design: Prospective observational study at a tertiary care pediatric endocrine unit where children with T1D with disease duration of more than 1 year were included in the study. We present here a 3 year follow up. Apart from regular care, detailed follow-up of diabetes on yearly basis is carried out including clinical history, anthropometry, bone age (by TW3 method) and HbA1c. Chronological age (CA), bone age (BA) and disease duration were noted. National references were used to calculate Height Z score for chronological age (HAZ) and height Z score for bone age (HBZ). All data were recorded and analysis was performed with SPSS 25.0.

Results: A total of 78 (42 boys and 36 girls) children were included in the study. The mean age at baseline was 10.3 ± 3.6 yrs with mean disease duration at baseline of 3.6 ± 3.1 yrs. HAZ at baseline, 1 yr, 2y and 3 yr of follow-up were -0.78 ± 1.1 , -0.82 ± 1.1 , -0.72 ± 1 and -0.87 ± 0.9 for boys and -0.7 ± 1.2 , -0.64 ± 1.1 , -0.65 ± 1.1 and -0.2 ± 1.3 for girls respectively. HBZ was -0.68 ± 1 , -0.47 ± 1 , -0.48 ± 1.2 and -0.51 ± 1.1 among boys and -1 ± 0.9 , -0.7 ± 0.7 , -0.7 ± 0.9 and -0.28 ± 1.6 among girls at baseline, 1 yr, 2yr and 3 yr respectively. CA and BA had a significant co-relation ($r=0.82$, $p<0.05$). From baseline to the 3 year follow-up, there was a significant decline in HAZ in boys while girls showed an improvement ($p<0.01$). HBZ improved in boys significantly but not in girls ($p<0.05$ and $p=0.95$). Ratio of CA and BA showed a decline from 1.02 ± 0.15 to 1.05 ± 0.13 ($p<0.05$) in boys and in girls 0.98 ± 0.14 to 1.01 ± 0.14 ($p=0.45$). HbA1c had a negative co-relation with HAZ and HBZ but was not statistically significant.

Conclusion: Children with diabetes were short in comparison with reference growth data. In boys the advancement in bone age was significantly slower compared as to the chronological age. It is critical to monitor growth in relation to skeletal maturity in children with diabetes.

P2-39

Bone mineral status in adults with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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Introduction: 21-Hydroxylase deficiency is the most frequent inborn error of steroidogenesis causing congenital adrenal hyperplasia (CAH). Bone status is affected by chronic glucocorticoid therapy and excess androgen exposure in patients with CAH. Our objective is to evaluate the bone mineral metabolism and density in adulthood in a Tunisian cohort.

Subjects and Methods: We underwent a prospective study of 26 patients over 16 years of old with CAH.

Results: The cases included 26 patients (M: 11, F: 15) with CAH due to 21-hydroxylase deficiency with a mean age of 27.4 years (16.5-48 years). Eighteen patients had the classical CAH form and the remaining 8 patients had the non-classical form. The mean body mass index was 26.9 ± 4.27 kg/m² (20.3-34.8 kg/m²). The most commonly used drug was hydrocortisone which was used by 21 cases. Five cases had been managed on dexamethasone alone. The mean serum calcium level was 2.32 ± 0.16 mmol/l (1.91-2.55 mmol/l) and mean serum phosphorus 1.08 ± 0.15 mmol/l (0.8-1.48 mmol/l). The mean parathormon was 89.8 ± 29.4 pg/ml (4.9-141 pg/ml) and mean 25 hydroxy vitamin D was 15.8 ± 8.6 ng/ml (4-32 ng/ml). Vitamin D deficiency was observed in twenty two cases. Only one patient 23.5 years-old with the classical CAH form had an anterior non-traumatic vertebral compression fracture L1-L2. Of the 25 studied patients by bone densitometry, 10 showed bone demineralization: 1 case of trabecular osteoporosis and 9 cases of osteopenia.

Conclusion: It seems difficult to conclude on the bone status of adult patients with 21-hydroxylase deficiency. Most studies are retrospective with heterogeneous population that includes limited number of patients, often under the age of 50. However, it seems that bone density is most often preserved in patients who benefit from recent treatment protocols using more physiological doses of glucocorticoids.

P2-40**Reduced bone mineral density in children with inflammatory bowel disease without exposure to Corticosteroid treatment**

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Objectives: Bone mineral density is reduced in children and adolescents with inflammatory bowel disease (IBD). The exact cause of this reduction is not known and is often attributed to corticosteroid use. The aim of the study was to evaluate bone mineral density in children with IBD without previous corticosteroid exposure.

Methods: Twelve children aged 8-17 years with IBD (8 with Crohn's disease and 4 with ulcerative colitis) underwent dual-energy x-ray absorptiometry (DEXA). Data on growth and pubertal development, disease activity, and calcium metabolism were recorded. Bone mass measurements were performed and z-scores were adjusted for bone age.

Results: Four of the 12 patients (33.3%) had lumbar spine bone mineral density z score less than -1 (three had a z score less than -2). The same percentage (33.3%) of children had total bone mineral density z scores less than -1 (two had z score less than -2). The subjects with IBD had significantly reduced mean lumbar spine bone mineral density z-scores ($P = 0.01$) and most of them had delayed puberty. 40% of children had 25OHvitD levels ≤ 20 ng/ml. There was not any association between bone density and children's auxological data or 25OHvitD levels.

Conclusion: A reduction of bone mineral density is common in children and adolescents with IBD. The inflammatory disease contributes to impaired bone mass and delayed puberty may constitute one of the mechanisms

P2-41**A clinical dilemma in the detection of paediatric hypophosphataemia**

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Background: In paediatric patients with metabolic bone diseases, measurement of the concentrations of minerals including inorganic phosphate is often indicated, and hypophosphataemia is a clinically manageable biochemical disorder. The clinical interpretation of plasma or serum phosphate concentrations depends, to a certain extent, on the age- and gender-specific reference intervals applicable to the laboratory methods employed.

Whereas harmonised phosphate reference intervals based on consensus have been published by professional groups, recent large-scale prospective studies have established paediatric reference intervals for many analytes by recruiting healthy young subjects from their populations and using the direct method for establishing reference intervals.

Methodology: A literature search was conducted to identify

(1) prospective, a priori studies for the establishment of paediatric reference intervals, and (2) published consensus paediatric phosphate reference intervals. The age- and gender-specific phosphate reference intervals from these sources were compared and contrasted with one another.

Results: We have identified two sources of harmonised paediatric phosphate reference intervals based on consensus among healthcare professionals, i.e. the Australasian Association of Clinical Biochemists (AACB) and the Pathology Harmony Group (United Kingdom), and four separate well-designed, large-scale prospective studies for the direct establishment of paediatric reference intervals for plasma/serum phosphate concentrations.

The consensus reference intervals for paediatric phosphate concentrations from the AACB and the Pathology Harmony Group are partitioned according to age but not gender. Although prospective studies on healthy paediatric populations have shown that in general, phosphate concentrations in plasma and serum gradually decrease from birth until adulthood, the Pathology Harmony Group currently recommends a single age partition for plasma and serum phosphate concentrations in both genders from 1 to 16 years of age. Among the prospective studies, age-specific upper and lower reference limits in boys are generally either the same as or slightly higher than the corresponding reference limits in girls. From birth up to 13 years of age, all consensus lower reference limits (RLs) for phosphate in both genders recommended by the AACB and the Pathology Harmony Group are numerically lower than the corresponding age- and gender-specific phosphate RLs established using direct methods in the above four prospective studies.

Conclusion: Age-partitioned phosphate reference limits are important for clinical practice in detecting paediatric hypophosphataemia. The harmonised paediatric phosphate RLs based on consensus and published by the AACB and the Pathology Harmony Group may lack diagnostic sensitivity in detecting mild to moderate hypophosphataemia especially in young children.

P2-42**Stuve-Wiedemann syndrome: a case report without osteorosis**

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Stüve-Wiedemann syndrome (SWS) is an autosomal recessive disorder characterized by bowing of the long bones and other

skeletal anomalies, neuromuscular abnormalities, dysautonomic symptoms, and respiratory and feeding distress usually resulting in early death.

We report a girl, aged 6 years, with SWS. We measured bone mineral density in the lumbar spine, using dual-energy x-ray absorptiometry (DXA) with a densitometer (Hologic). The result is expressed as z scores (the number of standard deviations from the mean value for persons in the general population matched for age, sex, and race). It was higher than + 2.

Molecular diagnosis was a homozygous mutation in exon 7 of leukemia inhibitor factor receptor (LIFR) gene located on 5p13-p12 (c.2074C>T (p.Arg692*) (p.R692*)). Her parents were *heterozygous* for this mutation.

Survival beyond the first 3 years in SWS has been reported limitedly. Our patient is still alive at the age of 6 years. As far as we know, this is the first case of SWS with spontaneous fractures without osteoporosis.

P2-43

A rare form of Vitamin D Receptors dysfunction (vitamin D-dependent rickets type II) with alopecia.

A Case Report

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Introduction: VDDR II is an autosomal recessive disorder caused by a defect in the vitamin D receptor gene located on chromosome 12q12–q14. Thus far, 13 mutations have been identified.

It is characterized by hypocalcemia, secondary hyperparathyroidism, and early onset severe rickets. Here we report a case of a severe form of rickets associated with alopecia.

The Case: This 23-month-old boy was born at term to consanguineous parents. He was referred with persistent hypocalcemia; not responding to oral calcium and vitamin D therapy, progressive alopecia capitis and macrocephaly. He had delayed gross motor development with deformed wrist and ankle joints and severe leg bowing. He had been on vitamin D (1400 units/day) and calcium prescribed for 2 months. He did not have any gastrointestinal or urinary symptoms, He did not develop any seizure, abnormal movement recently or impaired consciousness. He had no family history of vitamin D/calcium abnormalities.

Clinically has alopecia capitis, closed fontanelle. His weight = 12.15kg (0.01SD), length = 79.5cm (-2.7 SD) and head circumference 48.8cm (0.48SD). He had parietal and frontal bossing, rachitic rosaries, Harrison sulcus, widening of the wrist and bowing of the distal radius and ulna and bowing of the femur and tibia. His system examination was otherwise unremarkable.

The radiologic investigation revealed extensive cupping, fraying and splaying of the distal metaphysis of both femora and proximal and distal metaphysis of the tibia and fibula with diffuse osteopenia and cortical thinning of the shafts of the tibia and fibula.

The patient was started on oral elemental calcium (100 mg/kg/day) divided q8 hourly and alfa calcidiol 2 mcg daily. Monitoring showed no improvement in biochemical or radiological parameters after 4 weeks.

Conclusion: Therapy with a high dose of vitamin D analogues with oral calcium was not effective in our case. Higher doses of oral calcium and/or intravenous calcium therapy has been discussed with the parents as a next possible therapy.

	Before treatment	4 weeks after starting the treatment	Normal values
Serum total calcium	1.72 mmol/L	1.62 mmol/L	2.32-2.64
Serum phosphate	1.11 mmol/L	1.31 mmol/L	1.45-2.33
Serum creatinine	15 mcmol/L	16 mcmol/L	17-36
Serum alkaline phosphatase	1,531 IU/L	1,521 IU/L	134-315
Serum Magnesium	0.81 mmol/L	0.86 mmol/L	0.70-1.00
25 OHD level	69 nmol/L		
PTH – intact molecule	46.3 pmol/L	52.7 pmol/L	1.3-5.8
1,25 OH₂ vit D	870pmol/l		58-207

P2-44**Cinacalcet experience in hypercalcemia due to CaSR mutation**

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Introduction: Heterozygous inactivating mutations of the CaSR gene (CaSR) generally result in mild, asymptomatic hypercalcemia in the familial hypocalcuric hypercalcemia syndrome. Homozygous inactivating CaSR mutations end up with neonatal severe hyperparathyroidism. Calcimimetics are drugs that interact with the transmembrane part of CaSR and make the receptor more sensitive to calcium. Cinacalcet, a type II calcimimetic, suppresses PTH levels and increases renal calcium excretion.

Case: A 7-years 9 months-old girl presented with hypercalcemia. She was diagnosed with hypercalcemia because of vomiting and abdominal pain when she was 1,5 years old. She had taken hydration, diuretic, steroid and pamidronate treatments. Genetic analysis revealed a p.R185Q (c.554G> A) heterozygote mutation and p.A986S (c.2956G> T) polymorphism in the CaSR gene. 1 mg / kg / day furosemide treatment was learned. On physical examination, weight: 24.4 kg (25-50p), height: 118.7 cm (10p), blood pressure 90/60 mmHg, and other system examinations were normal. When Ca: 14.1 mg / dl was considered, i.v hydration, i.v furosemide and prednisolone treatments were started. Despite these treatments, Ca: 13,2 mg / dl, 1x30 mg / day cinacalcet treatment was started. Ca: 12.2 mg / dl at the 24th hour of treatment and Ca: 11.6 mg / dl at the 96th hour. She was treated with cinacalcet for 3 years and her calcium level was between 11,1-12,3 mg / dl. No side effects were observed. Renal ultrasonography was normal.

Result: Cinacalcet treatment has been reported to be effective in the treatment of severe hypercalcemia due to CaSR mutations, especially in the neonatal period. Calcium levels of the patient were at the upper limit of normal for 3 years and no side effects were observed. In cases of hypercalcemia resistant to other therapies, treatment with cinacalcet may be given.

P2-45**Two siblings with hypophosphatemic rickets: SLC34A3 gene mutations with different clinical phenotypes**

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Background: Hereditary hypophosphatemic rickets with hypercalciuria(HHRH; OMIM: 241530) is a rare autosomal recessive disorder, which is the result of loss-of-function mutations in the sodium-phosphate-cotransporter NPT2c. This disorder is characterized by renal phosphate(Pi) wasting, hypercalciuria, increased 1,25 (OH)₂D levels and decreased parathormone(PTH) levels. Here we report the clinical features of two siblings with HHRH, confirmed with molecular diagnosis.

Case Reports: One of the two siblings born to first-degree-consanguineous parents, *Case 1* is a 16-year 9-month old boy, and *Case 2* is a 8-year 8-month old girl. They were both referred to our outpatient-clinic due to bowing legs and difficulty in walking. In addition, *Case 1* suffered fracture on his right femur, which was the fourth fracture on his leg. Birth histories and developmental-milestones were normal in both of them. At the referral time, weight, height and body mass index(BMI) of *Case 1* were 48 kg (-2.6 SDS), 155.3 cm (-3.0 SDS) and 19.9 kg/m² (-1.0 SDS) respectively, the puberty was Tanner 5. The anthropometric measurements of *Case 2* were 24.7 kg (-0.7 SDS), 129.9 cm (-0.1 SDS), 14.6 kg/m² (-0.9 SDS) respectively, puberty was Tanner 1 and genu valgus deformity was remarkable on physical examination. Laboratory examination of *Case 1* revealed serum calcium (Ca) 9.7 mg/dl, phosphorus (P) 1.7 mg/dl, alkaline-phosphatase (ALP) 360 U/L, 25 OH-D-vitamin 9.2 ng/ml, PTH 8.2 pg/ml (12-65) and 1-25 D-vitamin 88 pg/ml (26-95). Bone mineral density at the spine (L1-L4) was measured as 0.697 g/cm² (corrected z-score +0.7). Laboratory examination of *Case 2* revealed Ca 10.1 mg/dl, P 3.3 mg/dl, ALP 435 U/L, 25-OH-D vitamin 14.5 ng/ml and PTH 13.4 pg/ml. Tubular phosphate reabsorptions were 88% in both cases. Two siblings had also hypercalciuria and on follow-ups bilateral renal calculi in *Case 1* and bilateral Grade1 nephrocalcinosis in *Case 2* were detected. Metabolic tests and arterial blood gas test of cases were in normal ranges. In the light of these findings, HHRH was considered as pre-diagnosis and SLC34A3 gene analysis was performed. Genetic analysis revealed homozygous mutation in SLC34A3 c.756G>A (p.Gln252=) and c.1335+2T>A p.?(splice donor variant). After oral phosphorus treatment clinical and biochemical improvements were observed in both cases

Conclusion: Hereditary hypophosphatemic rickets with hypercalciuria is a rare cause of hypophosphatemic rickets. Diagnosis is important for the treatment. The clinical phenotype due to mutations in the SLC34A3 gene may vary even among effected siblings regarding to severity of hypophosphatemia, short stature, deformity in extremities and also frequency fractures.

P2-46**Seasonal 25-hydroxy Vitamin D3 variations in school-aged children from Santiago de Chile**

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Introduction: The main role of Vitamin D (VitD) is the regulation of calcium, which is also regulated by the parathyroid hormone (PTH), and phosphate metabolism. The main source of the more biologically active 25-hydroxy-Vitamin D3 (25OHVitD3) comes from the action of ultraviolet light on the skin.

Aim: To determine if there are differences in concentrations of 25OHVitD3, calcium and PTH in school-aged children throughout the four seasons

Subjects and Methods: Children 5-8 years old with no Vitamin D supplementation were recruited in different urban areas of Santiago de Chile (latitude -33.4372). 25OHVitD3 was measured

	Summer (n=41)	Autumn (n=28)	Winter (n=35)	Spring (n=29)	P (Anova)
Calcium (mg/dL)	9.92 ±0.37	9.89 ±0.26	9.89 ±0.28	10.00 ±0.27	0.425
PTH (pg/mL)	25.9 ±6.3	36.1 ±12.6	36.9 ±9.4	36.7 ±11.3	<0.001
25OHVitD3 (ng/mL)	31.2 ±6.7	24.2 ±4.9	21.5 ±5.7	25.7 ±7.7	<0.001

by Liquid Chromatography-Mass Spectrometry, PTH by an automated immunoassay and calcium by a colourimetric automated assay. A One-way ANOVA was conducted to compare the 25OH-VitD3, PTH and calcium concentrations and the Tukey's multiple comparison test to establish which mean was different from the other.

Results: 133 children were recruited during the four seasons by chance. No differences were found in age ($p=0.419$), height Z-score ($p=0.466$) or Body Mass Index ($p=0.962$) among the groups. Results:for calcium, PTH and 25OHD3 are shown in the table above.

Compared to summer, mean differences in 25OHVitD3 concentrations were as follows: 5.4 ng/mL higher than in spring (95% CI: 1.3-9.5 ng/mL, $p= 0.0045$), 6.9 ng/ml higher than in autumn (95% CI: 2.8-11.1 ng/mL, $p= 0.0001$) and 9.6 ng/mL higher than in winter (95% CI: 5.7-13.5 ng/mL, $p <0.0001$). In comparison to summer, PTH concentrations were 10.8 pg/mL lower than in spring (95% CI: 5.3 to 16.3 pg/mL, $p <0.0001$), 8.3 pg/mL lower than in autumn (95% CI: 2.7 to 13.9 pg/ mL, $p= 0.001$) and 11.1 pg/mL lower than in winter (95%CI: 5.9 to 16.3 pg/mL, $p <0.0001$).

Conclusion: In autumn and winter, 25OHVitD3 concentrations decrease importantly, triggering an increase in PTH, in order to maintain calcium concentration. In regions where no Vitamin D supplementation is performed but where relatively prolonged winters are observed, as in Santiago de Chile and further south, reduced exposure to sunlight can lead to lower levels of vitamin D at least in school-aged children.

P2-47

Vitamin D Deficiency among Children with Malignancy

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Introduction: Vitamin D deficiency is one of the most common nutritional deficiencies in the world. This vitamin plays an important role in cellular functions. Studies have shown that vitamin D plays a very important role in preventing the growth of cancer cells.

Only a few studies have been done worldwide in relating the Vitamin D levels in pediatric cancer patients to the general population. The aim of this study was to compare the Vitamin D levels in a group of Children with Malignancy to that of the control group.

Materials and Methods: Considering the criteria for entering and leaving the study; all children with malignancy referred to the Oncology Clinic of the Children's Hospital of Tabriz - Iran, after

describing the purpose of the study and its implementation to the parents of children, and obtaining consent Conscious letters from parents were entered in the study.

Serum levels of Ca, P, AlkP, and vitamin D were measured by immune-chemilumino-metric assay in 100 children (50 cases and 50 controls) over a 12 months period.

Results: In this study, there was a significant difference between the mean values of vitamin D between the two groups ($p = 0.001$). The mean level of vitamin D in case and control group was 17.63 ± 4.75 and 30.05 ± 14.49 ng/ml respectively.

A significant relationship was found between the levels of vitamin D in various types of malignancy ($P = 0.001$). It was also found that children with ALL had a greater chance (26%) and children with hepatoblastoma had the least chance (2%) for developing Vitamin D insufficiency.

Conclusion: Our study showed an increased prevalence of Vitamin D insufficiency in children with cancer and the Highest rate of incidence of the malignancy related to ALL. we suggest routine measurement of Vitamin D levels in children with cancer and subsequent supplementation.

Keywords: Childhood, Malignancy, Vitamin D

P2-48

Novel mutation of the prkar1a gene in a girl with clinical diagnosis of Pseudohypoparathyroidism

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Introduction: Despite the high detection rate of GNAS molecular defects, about 30% of patients with a clinical suspect of PHP/AHO still lack a confirming molecular diagnosis. Mutations in genes encoding proteins crucial for cAMP-mediated signaling have been recently detected in a small subset of patients negative for GNAS defects, showing a phenotypic overlap between PHP and Acrodysostosis.

Clinical Case Presentation: We report on a case of acrodysostosis associated with mutation in the PRKAR1A gene in a girl with a clinical diagnosis of PHP1A. Our female patient was born as the second child of healthy unrelated parents at 38 weeks of gestation by caesarian section following a pregnancy complicated by oligohydramnion with birth weight 2,120 g and length 51 cm. A 6-year-old girl was referred to our pediatric endocrinology clinic for obesity. Physical examination revealed broad face, widely spaced eyes, maxillonasal hypoplasia, small broad hands and feet,

and subcutaneous ossifications at her right leg. Her weight was 25 kg (90th percentile), height 112,3 cm (25th to 50th percentile), and body mass index was 19,8 (>97th percentile). Radiography of the hands and feet showed brachydactyly and cone-shaped epiphyses. Celiac disease was diagnosed at the age of 6,5 years. Resistance to TSH was documented by increased TSH (9,6 mIU/L) with normal thyroxine level, absence of anti-thyroid antibodies and presence of normal thyroid scan at the age of 6,5 year. Hormonal resistance to PTH was documented at the age of 9 years, as indicated by increased PTH level (129 pg/ml) in the presence of normale serum calcium (2,4 mmol/L) and increased serum phosphate (1,8 mmol/L). The presence of genetic/epigenetic defects affecting GNAS locus had been excluded. After the age of 10 progressive growth failure with lack of pubertal spurt was documented. No behavioral disorders, nor learning disability were noticed. According to the growing knowledge on Gsa-cAMP signaling-linked disorders, screening of PRKARIA and PDE4D in a large series of patients clinically diagnosed with PHP1A/AHO but negative for GNAS defects was done. Sanger sequencing analysis of coding exons 2-11 in our patient unraveled a previously undescribed heterozygous missense variant (c.625A>G) affecting exon 7.

Conclusion: The molecular and clinical overlap among these Gsa-cAMP signaling-linked disorders indicates the need for different classification models and for a deeper investigation of the mechanisms through which defects of the cAMP signaling cascade cause either common or specific clinical phenotypes in order to elaborate patient-specific algorithms.

P2-49

Successful treatment with enzyme replacement therapy in a girl with severe infantile Hypophosphatasia

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Background: Infantile Hypophosphatasia (HPP) is an inborn error of metabolism characterized by low serum alkaline phosphatase activity caused by loss-of-function mutations within the ALPL-gene encoding the tissue nonspecific isoenzyme of ALP (TNSALP). TNSALP controls skeletal and dental mineralization by hydrolyzing inorganic pyrophosphate, a potent inhibitor of bone mineralization. Patients develop substantial skeletal disease, failure to thrive, and sometimes vitamin B6-dependent seizures before 6 months of age. Without treatment, HPP results in 50–100% mortality, typically from respiratory complications.

Presenting Problem: We present a 3 months old girl with infantile HPP caused by 2 heterozygous mutations in the ALPL gene. At the age of six weeks she presented with a lack of weight gain because of vomiting and respiratory insufficiency. Clinical investigations showed rhizomelia of the upper arms and femora,

short stature, broad nose bridge, high forehead, a bulged fontanelle and muscular hypotension. A single cerebral seizure terminated spontaneously. Laboratory examinations revealed a very low serum ALP activity and a high urinary excretion of phosphoethanolamine. Radiographic findings include hypomineralization with cup-shaped distensions of the metaphysis and irregular zones of ossification.

Clinical Management: Starting enzyme replacement treatment 2 mg/kg s.c. every other day was associated by a supportive therapy with oxygen, enteral nutrition through nasogastric tube, physiotherapy and supplementation of calcium, pyridoxine and analgetics. As a result of therapy x-rays showed an increase of bone mineralization. Stabilization of the chest wall led to a normal breathing pattern without need of oxygen support after 8 weeks. After improvement of vomiting tube-feeding could be weaned after 4 weeks with good weight gain. Muscular strength and neurological function improved also.

Discussion: Infantile hypophosphatasia is extremely rare and may be life threatening.

Our case demonstrates that treatment with the recombinant enzyme therapy led to an improvement in muscular hypotonia, neurological problems and skeletal mineralization and therefore, respiratory function, growth and weight normalised.

P2-50

Bone Mineral Density in Children with Type 1 Diabetes Mellitus (T1DM) and Analysis of Possible Factors Affecting Their Bone Health; A controlled study

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Type 1 diabetes mellitus (T1DM) may be associated with reduced bone mineral density (BMD). Possible pathogenic mechanisms include impaired bone anabolic effect due to decreased insulin and insulin-like growth factor 1 (IGF-I). In addition, hyperglycemia can impair osteoblast function.

We measured anthropometric data, glycemic control (HbA1C), insulin dose /kg, calcium, PO4 and alkaline phosphatase and BMD by (DEXA scan at the spine (L2-L4) and at the Femur) in 25 children and adolescents with T1DM on insulin therapy for > 5 years and poor glycemic control (HbA1C > 8.5%) attending the diabetic clinic in Alexandria University Children's Hospital, Egypt and compared them . Their data were compared with 5 children with IDDM with good glycemic control and 30 apparently healthy children of matched age and sex.

Results:

Table 1 : BMD and biochemical data of T1DM versus controls

	Ca	PO4	ALP	BMD Total	Femur	Spine
IDDM-Bad Control	9.44	4.07	268.00	-1.46	-0.41	-1.37
	2.12	1.24	120.00	1.30	1.28	1.37
IDDM-Good control	9.38	3.60	232.00	-0.74	-0.14	-0.70
	0.61	0.75	89.00	0.74	0.68	0.91
Normal Children	9.20	4.29	176.00	-0.58	0.12	-0.49
	0.44	0.36	78.00	1.15	1.27	1.15
ANOVA- P value	0.45	0.07	0.001*	0.02*	0.29	0.03*

Table 2 : Clinical, biochemical and BMD T1DM with good control vs bad control.

	Age	Duration of T1DM	T- Stage	Insulin/kg	HbA1c	HtSDS	BMI.SD	GFR	BMD-Fem	BMD-Spine
Bad control	12.42	7.58	2.33	1.06	11.15	-0.93	0.27	149.54	-0.41	-1.37
	3.35	2.79	1.69	0.30	2.84	1.20	1.00	42.91	1.28	1.37
Good control	10.9	8.80	2.40	1.06	7.80	-0.80	0.49	137	-0.14	-0.70
	3.22	1.60	1.50	0.22	0.62	0.92	1.30	17.6	0.68	0.91
M-W-P	0.27	.27134	.1770	.27134	.0002*	0.78	0.27	0.37	0.08	0.05*

BMD was significantly lower in children with T1DM compared to controls and spine BMD was lower in T1DM with high HbA1C vs those in good control. Serum ALP level was higher and phosphate was lower in children with bad control versus other groups. BMD was correlated with HtSDS ($r = 0.34$, $p = 0.056$) but not with age of patients, HbA1c, duration of disease, age or insulin dose.

Conclusion: Decreased BMD is common in children with T1DM especially those with bad control. We recommend the assessment of BMD in children with T1DM on long term insulin therapy for the early management of their bone health.

the mutations causing HPP. It has been shown that asfotase alfa treatment mineralizes the skeleton and improves respiratory function and survival in severe forms of hypophosphatasia.

The newborn was evaluated for respiratory failure and generalized hypotonia after birth. Diagnosis of HPP was based on low serum ALP activity, high levels of substrates of tissue-nonspecific isoenzyme of alkaline phosphatase and radiologic findings. On day 21 after birth, enzyme replacement therapy using asfotase alfa (2 mg/kg three times per week, subcutaneous injection) was started. We were able to discharge our patient when he was 7 months old. His respiratory support was gradually reduced and skeletal mineralization improved during treatment. We increased the dose when he 13 month-old due to incomplete resolution of radiological rickets findings. He has been no need any respiratory support after 18 month old. He was operated for craniosynostosis at 23 month old. No mutation was detected in the *ALPL* gene by all exon sequencing, and additional analysis was done by quantitative polymerase chain reaction. As a result, a novel homozygote duplication encompassing exons 2 to 6 was detected.

Early diagnosis and rapid intervention with enzyme replacement therapy is life-saving in the severe form of hypophosphatasia. Craniosynostosis can occur in these patients although early enzyme replacement therapy. Quantitative polymerase chain reaction can detect duplications if a mutation cannot be detected by sequence analysis in patients with hypophosphatasia.

P2-51

Perinatal form hypophosphatasia caused by a novel large duplication of *ALPL* gene and two year follow-up under enzyme replacement therapy; a case report

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Hypophosphatasia is a rare disease caused by mutations in the gene encoding tissue- nonspecific isoenzyme of alkaline phosphatase. Duplications of the *ALPL* gene account for fewer than 1% of

P2-52**A rare cause of hypophosphatemia: Raine Syndrome**

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Background: Raine Syndrome (RS) is characterized by hypophosphatemia and typical facial dysmorphic features. Subperiosteal thickening and diffuse generalized osteosclerosis are the most common radiological findings. Biallelic loss of function mutations in *FAM20C* gene cause RS and by reduction of the transcription of DMP1 leads to FGF23-related hypophosphatemia. Here we present a new case with RS.

Case: A 9-month-old male patient on a home-type ventilator was referred for hypophosphatemia. He was born with a weight of 3800 gr to non-consanguineous parents. Prenatal USG demonstrated nasal bone agenesis. He had tracheostomy, percutaneous endoscopic gastrostomy and ventriculoperitoneal shunt operations at 48 days, 5.5 and 9 months of age, respectively. Family history was unremarkable. At presentation, his height, weight and head circumference were at -1.1, -2.14 and -0.62 SDS, respectively. A large anterior fontanel (5x6 cm), frontal bossing, exophthalmos, hypoplastic nose, high arched palate, low set ear, triangular mouth, and corneal opacification were detected on physical examination. The ophthalmological examination was consistent with optic atrophy.

On laboratory evaluation: Ca:9.6mg/dL (9-11), PO4:2.0mg/dL (4-6.5), ALP:950U/L (116-450), 25OHD: 28ug/L (30-100), 1,25OHD:107pg/mL (24-86), PTH:84.5ng/L (15-65), Cre:0.12mg/dL (0-0.42), Mg:2.0mg/dL (1.8-2.6), U-Ca/Cre:0.22mg/mg (0.03-0.8), U-PO4/Cre:0.94mg/mg (<5.2), TRP:94% (85-100), TmP/GFR:2.31 (4.8-8).

Serial skeletal X-rays revealed diffuse osteosclerosis at birth which was gradually resolved by the age of 5 months and medullary space of long bone could be distinguishable with bone-in-bone appearance. At 9 month of age hand X-ray revealed cupping of ulna with loose radial bone margin with minimal fraying and osteopenia. Cranial CT scan showed bilateral periventricular calcification with cerebral atrophy. The clinical, laboratory and radiological examinations were consistent with RS. Molecular analyses revealed a compound heterozygous mutation in *FAM20C* gene (a known pathogenic mutation, c.1645C>T, p.Arg549Trp.; and a novel insertion, c.953_956insACAGGTGAGCCC)

Conclusion: We described a novel variant in *FAM20C* gene contributing to RS phenotype. Although rare, RS should be considered in differential diagnosis of FGF23 related hypophosphatemia in patients with typical craniofacial abnormalities.

P2-53**Idiopathic infantile hypercalcemia: Mutations in *SLC34A1* and *CYP24A1* in two siblings and fathers**

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Background: Both *CYP24A1* and *SLC34A1* gene mutations are responsible for idiopathic infantile hypercalcemia (IIH). Whereas loss-of-function mutations in *CYP24A1* (25-OH-vitamin D-24-hydroxylase) lead to a defect in the inactivation of active 1,25(OH)₂-vitamin D₃, mutations in *SLC34A1* encoding renal sodium-phosphate co-transporter NaPi-IIa lead to primary renal phosphate wasting combined with an inappropriate activation of vitamin D. The presence of mutations in both genes has not been reported in the same patient until today.

Aim: Our aim is to show the clinical findings of the siblings as well as the parents who carry mutations in both genes.

Case Report: Case 1: Hypercalcemia was detected in a 13-month-old boy with urinary tract infection (UTI). Hydration and furosemide were given for hypercalcemia. Oral phosphorus solution was started since serum phosphorus and TRP was lower. All therapy was stopped when calcium and phosphorus were within normal.

Case 2: Hypercalcemia was detected in a 6-month-old girl with (UTI) (Table 1). High dose vitamin-D had been not given. Serum calcium normalized with hydration and furosemide (10.5 mg/dL).

Bilaterally medullary nephrocalcinosis was detected in both siblings. Serum Ca and P were within normal limits at follow-up in both siblings. Siblings and their parents all carry a homozygous stop codon mutation (p.R466*) in *CYP24A1*. Interestingly both siblings and the father also have a heterozygous splice-site mutation (IVS6(+1)G>A) in *SLC34A1*. Father has nephrocalcinosis at right kidney. Siblings' paternal aunt and paternal uncle also have nephrocalcinosis and, their paternal grandmother and grandfather was second cousin.

Conclusion: A bi-allelic loss-of-function mutation in the *CYP24A1* gene was identified as responsible for hypercalcemia, hypercalciuria and nephrocalcinosis. In addition, a heterozygous mutation in the *SLC34A1* gene although not being the main pathogenic factor, might contribute to the severe phenotype of both patients.

At the admission	Case 1	Case 2	Father	Mother
Weight,kg (SD)	10.5 (-0.01)	7.5 (0.11)		
Height,cm(SD)	77 (-0.42)	62(-1.17)		
Ca, mg/dL	16.7	17.3	9.8	9.5
P,mg/dL	2.3	3.8	4.7	2.9
ALP, IU	179	71	117	83
PTH, pg/mL (12-88)	<6	4.6	12	22.7
25OHD3, ng/mL (10-70)	6.9	18.91	11.2	16.4
1,25OHD3, pg/mL (19.6-65)	19.9	47.56	12.74	26.06
Spot Urine Ca/Cr	1.69	1.7	0.22	0.05
TRP, %	74	82	90.5	82

P2-54

Crouzon Syndrome: A rare case report of a 2-month old boy with micrognathia and proptosis

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Objective: To diagnose a 2-month old boy with micrognathia and proptosis.

Method: We summarized the clinical manifestations of the patient. Blood tests and imaging examinations were performed. DNA was isolated from peripheral blood cells. Whole exosome sequencing (WES) was conducted. Copy number variation (CNV) and loss of heterozygosity (LOH) was analyzed by Affymetrix CytoScan.

Result: The patient was 2 months and 16 days old. He was found proptosis and not able to track objects with his eyes one month ago. His mother had gestational diabetes and subclinical hypothyroidism during pregnancy. His body weight was 4.5kg, and head circumference was 36 cm. Physical examination showed protruding eyes; premature fusion of lambdoidal suture, sagittal suture and frontal suture; frontal fontanelle 2cm*2cm; ocular hypertelorism; low-set ears; a high, narrow palate; a long philtrum; a small lower jaw; laryngeal stridor; crossed extensor reflex, Babinski's reflex and Moro reflex could not be triggered, while Knee-jerk reflex and incurvatum reflex were observed; no abnormalities were found in his limbs, fingers, toes and vertebrate. His blood gas, liver function, kidney function, thyroid function, lactic acid level, pyruvic acid level, levels of serum amino acids, levels of urine organic acids, and serum acylcarnitine levels were all normal. Brain MR scan showed enlarged left ventricle and dilated pericerebral space. Echocardiography showed multiple atrial septal defects. His hearing was normal and he had no retinopathy. There was no CNV and LOH detected in his DNA. WES revealed a *de novo* heterozygous c.1024T>A mutation leading to a p.Cys342Ser mutation in the FGFR2 gene, which was a hotspot of mutation and reported to be related with Crouzon syndrome and Pfeiffer syndrome.

Conclusion: According the results above, this patient was diagnosed as Crouzon syndrome, which is a rare genetic disorder and characterized by craniosynostosis. This rare case suggests that the diagnosis of rare diseases should be made in combinations of clinical characterization, examinations and genetic analysis.

P2-55

A novel missense COL10A1 mutation identified by next generation sequencing in a Chinese pedigree with Schmid metaphyseal chondrodysplasia

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We have examined a female child patient aged about 3 years and 8months old to confirm the diagnosis of Schmid metaphyseal chondrodysplasia (SMCD) at the Genetics out-patient department, Children's Hospital Affiliated to Zhengzhou University. The child was diagnosed with the abnormal phenotypic characteristics who showed short-limbed dwarfism, bowed legs, waddling gait and genu varum. Based on the child's family history, during the early stages, the child was misdiagnosed with rickets inflicted by Vitamin D deficiency. However, the next generation sequencing performed on the isolated peripheral blood-DNA samples of the patient has confirmed the novel missense mutation with the heterozygous c.2020G>A substitution occurred at the COL10A1 gene. This novel COL10A1 gene mutation was also confirmed by the Sanger DNA sequencing in the proband, her younger male sibling and mother. Furthermore, a follow-up examination of the patient's clinical manifestations, as well as the Radiograph test results have confirmed the incidence of Schmid metaphyseal chondrodysplasia (SMCD), an autosomal dominant genetic disorder in the patient. To the best of our knowledge, we found the patient and her younger male sibling(aged 1 year and 5 months old) are the youngest children in China to get affected with the SMCD preceded by this novel mutation discussed above. Since the medical symptoms of the SMCD are closely resembling rickets in young children; the physicians would often get misled with the incorrect diagnosis of rickets in young children. We recommend the next generation sequencing in accordance with the other recorded clinical manifestations of SMCD and the Radiograph tests performed in this study as the preferred diagnostic module for the early diagnosis and treatment of SMCD in young children. Further, identification of this novel mutation in the COL10A1 gene could precede the physicians with a better understanding of the severity of SMCD symptoms associated with the COL10A1 gene mutation and therefore its early treatment.

P2-56**A case report of a girl with short stature has Iaron syndrome and spondyloepimetaphyseal dysplasia**

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20 months old girl has frequent hypoglycemas, protruding forehead(frontal bossing), sunken bridge of the nose (saddle nose), and a blue tint to the whites of the eyes (blue sclerae). short limbs compared to the size of her torso, as well as small hands and feet, fragile thin hair,short limbs, Genu varum, Brachydactyly,malar flattening, motor delay, delayed teeth eruption, when plotted to growth chart height found far below the third centile for age,sex,population, Hre laboratory investigations were normal a part from low IGF1 31- ng/ml (58-282), IGFBP3 1602- ng/ml (2010-5432), skeletal survey of the pt showed:chest narrowing, short ribs, and broad and short bones in the extremities and pelvis, small foramen magnum, short femoral neck, flared metaphysis, Molecular genetic analysis of whole exome sequencing(WES) showed a result of: clinically relevant variants with significant phenotypic overlap in the baby..

1-Gene :GHR

omim-p:604271/262500

transcriptNM_000163,4

variant c.positionc.281G>A

variant p.position:p.(Trp94)

zygosity:homo

ACMG class:pathogenic

2-Gene:ACAN

Omim-p: 612813/608361/165800

transcript:Nm_013227,3

variant c-position:c.1432G>T

variant p.positionp: p.(val478Phe)

zygosity: homo

ACMG: uncertain significance

interpretation:mutations in GHR is AD to recessive partial GH insensitivity and AR Laron syn/dwarfism

WES identified homo Z nonsense variant as above in results in exon 5 of the GHR gene,wich is not described befor in any darabase.

It also showed Homo missense variant as above in results in exon 8 of ACAN gene which has not been described in any database.

Taken together the detected homozygous GHR variant and homozygous ACAN variant may contribute to the mixed complicated clinical picture in this baby girl, making management is complicated.

Whether giving IGF1 analogue will be effective or not and how the patient will progress clinically over time.

P2-57**A novel mutation of pheX gene inducing X-linked Hypophosphatemia rickets, a case report**

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Introduction: X-linked hypophosphatemic rickets (XHR) is the most common form of hereditary rickets, with an estimated incidence of 1: 20.000 individuals. The main characteristic of the disease is excessive renal phosphate loss, which leads to hypophosphatemia with high phosphaturia and defective bone mineralization.

XHR results from mutations in the in the PHEX gene (Phosphate Regulatory Gene with Homology for Endopeptidases located on the X chromosome) located at Xp22.1. PHEX gene has 22 exons and is expressed mainly in the cell membrane of bones and teeth. Currently, at least 364 mutations have been identified, and are registered in the Human Gene Mutation Database.

The PHEX protein has 749 amino acids and three domains: N-terminal cytoplasmic, a single transmembrane region and a large extracellular domain. It functions as a transmembrane endopeptidase, with structure similar to membrane glycoproteins type II.

The protein has an indirect relationship with the hormone FGF23 (Fibroblast Growth Factor 23), which suppresses the action of genes that code for sodium-phosphorus co-transporters and also alters the expression of the vitamin D metabolizing enzyme, resulting in a decrease in the concentration of 1,25-(OH)D2.

Case Report: RRMJ, 2 years, mother G6P2A4, war referred to the pediatric endocrinology service due to reduction of growth rate, irritability, limb pain, skeletal malformations and bowing of legs. The biochemical parameters showed hypophosphatemia, elevated alkaline phosphatase, elevated PTH, normal calcium, increased urinary phosphorus.

Currently he is 6 years of age, and receives treatment with high doses of phosphate and 1,25(OH)2-vitamin D3, since he had 2 years and 2 months of age. The patient has difficulty following the prescription correctly due to frequent diarrhea and abdominal pain, and continues to grow at a percentile below the family target.

Molecular Analysis: New generation sequencing of the PHEX gene (OMIM 300550) was performed. We found the variant ChrX: 22.239.768 T>TG (c.1809dupG) which promotes the substitution of the amino acid Serine at position 604 by a Valine and generates a premature stop codon.

Conclusion: A novel pathogenic PHEX mutation was found: c.1809dupG, which caused early termination of translation and produced truncated protein that lead to exuberant clinical expression. Due to poor response to traditional treatment, it is scheduled to start treatment with Burosumab as soon as the drug is released in our country.

P2-58**Skeleton muscles and tissues metabolic activity in Greek adolescent PCOS**

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Background: The skeleton, which is strongly controlled by endocrine factors, has recently been shown to play an active endocrine role itself, specifically influencing energy metabolism. However, its role in polycystic ovary syndrome (PCOS) phenotype is underinvestigated.

Aim: Herein, we sought to identify novel factors involved in the regulation of both bone mass and whole-body homeostasis relevant to the disease.

Methods: In this pilot study, 10 PCOS (mean age 15.8 ± 3.2 years) vs 14 non-PCOS adolescents (mean age 15.1 ± 1.9 years), age and BMI matched underwent a body composition analysis by bioelectrical impedance, using a BIA phase-sensitive system (single-frequency 50 kHz). All participants did not have metallic implants of any kind in their body. The measurements took place in the Biomedical Research Foundation of the Academy of Athens (Stress and Metabolism Laboratory of the Clinical, Translational and Experimental Surgery Research Centre). The calculations were made non parametrically in SPSS 21.

Results: No differences in body cell mass (BCM) ($p=0.716$), extracellular mass (ECM) ($p=0.128$), skeletal muscle ($p=1.00$) were observed.

Conclusion: Metabolically active (BCM) and inactive (ECM) tissues of the body, as well as skeleton muscles show no differences in the two groups, perhaps due to the young of age. Future research should give a deeper insight to the subject investigating more markers by bioimpedance and/or biochemistry.

(OMIM 608125) mutation encoding xylosyltransferase II enzyme which is responsible from the first step of proteoglycan assembly is responsible for the pathogenesis. Phenotypical variability is associated with varying genetic expression. Two siblings diagnosed with spondyloocular syndrome treated with pamidronate therapy will be presented.

First patient was consulted for gait disorder, lumbar pain and inability to run at the age of 11. At the age of 1.5, she was operated for bilateral congenital cataracts, had nystagmus. She was diagnosed with retarded growth and development when she was 2.5 years old, retinal detachment at the age of 10. Third degree consanguinity was present. On physical examination her weight was 33.2 kg (25-50p), height was 125.6 cm (<3p). Disproportionate short stature was obvious (Upper/Lower ratio 0.76), pectus excavatum deformity, an increase in the lumbar lordosis and scoliosis, horizontal nystagmus and mild mental retardation were present. 25-OH vitamin D was deficient. Lateral vertebral scan revealed severe osteoporosis, vertebral corpus collapses and platyspondyly apparent in the thoracic segment. Lumbar bone mineral densitometry z-score was -3.6. Spondyloocular syndrome was suspected, *XYLT2* gene sequence analysis was performed, a homozygote new mutation on 11. exome (c.2548G>A (p.Asp850Asn)) was recognized, same homozygote mutation was detected in patient's seven year old brother. He was diagnosed with bilateral congenital cataracts, severe mental retardation, global motor and developmental delay, was unable to walk. He weighed 25 kg (50-75p), his height was 108 cm (<3p), proportionate short stature (upper/lower ratio:0.96), kyphosis, and increase in lumbar lordosis were noted. 25-OH vitamin D was deficient. Lateral lumbar X-ray revealed vertebral collapses and platyspondyly apparent in the thoracic and lumbar vertebrae. Lumbar bone mineral densitometry z-score was -2.3. Pamidronate (9 mg/kg/year) and vitamin D replacement therapy were initiated. After the first year of the therapy, bone mineral density z-scores have increased, vertebral corpus heights remained unchanged (BMD L1-L4 z-score were -1.8 and -0.5, respectively).

Spondyloocular syndrome is a rare disorder identified in 2001. Therapy options for the disease are limited and sufficient data on pamidronate therapy are lacking. Previously, three patients diagnosed with Spondyloocular Syndrome who received pamidronate therapy were reported, although bone mineral density has increased, new vertebral and long bone fractures could not be prevented. More data is required to understand disease course and determine therapy options.

P2-59**Spondyloocular syndrome: Presentation of two siblings diagnosed with the rare disease and the results of Pamidronate Therapy**

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Spondyloocular syndrome (OMIM 605822) is an autosomal recessive disorder characterized by skeletal complaints (osteoporosis, platyspondyly, multiple bone fractures), hearing loss and ocular symptoms (cataracts, retinal detachment). *XYLT2* gene

P2-60**Clinical and Genetic Characterization of Tunisian Children with Hereditary Hypophosphatemic rickets (HHR)**

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Background: Hypophosphatemic rickets (HHR) is a vitamin D-resistant rickets and results in children in variable degrees of delayed walking, waddling gait, leg bowing, enlarged cartilages, bone pain, craniostenosis and growth failure. There are both inherited and acquired forms, where FGF23-dependent forms with X-linked dominant hypophosphatemic rickets (XLH) head of the list is the most prevalent genetic form; molecular defects of the sodium-phosphate co-transporter NPT2c unrelated to a FGF23 disturbance may cause hypophosphatemic rickets with hypercalciuria (HHRH).

Patients and Methods: We report four cases of HHR and retrospectively studied the clinical features, laboratory findings, genetic defects, as well as responses to treatment : one case with yet described FGF23-activating mutation and three cases with a new mutation in the *SLC34A1* gene which encodes the type II sodium-dependent phosphate co-transporter NPT2a.

Results: four patients from 2 families one case with yet described FGF23-activating mutation and Three related cases with new mutation of the *SLC34A1* gene.

- In a girl who has been diagnosed at the age of 2 years and 10 months due to a gait disorder. The clinical-biological picture was compatible with hypophosphatemic rickets without hypercalciuria. The genetic study confirmed the diagnosis of dominant transmission hypophosphatemic rickets with mutation of the *FGF23* gene. This mutation is described in the literature. The evolution under treatment was marked by a partial improvement of rickets.
- Three children (two girls and one boy) who are from the same family. Hypophosphatemia was found in both children and parents, and in the latter especially in the father was also found the concept of urinary lithiasis. The diagnosis was made in the two sisters after the age of two years and their clinico-biological tables were compatible with hypophosphatemic rickets with hypercalciuria. At the brother's, the diagnosis was suspected at the age of two months in front of the family history and the discovery of a nephrocalcinosis. The genetic study carried out in one of the two girls as well as in the boy, confirmed the diagnosis of RHH with hypercalciuria, of recessive transmission, showing a homozygous mutation in the *SLC34A1* gene. At the present state of our knowledge, this is the first mutation in the *SLC34A1* gene causing HHRH, which is reported in the literature.

Conclusion: These results confirm the role of FGF23 in ADHR physiopathology and report for the first time HHRH caused by a homozygous *SLC34A1* mutation, thereby further documenting the key role of the renal cotransporter NPT2a in the phosphocalcic metabolism.

P2-61**Osteogenesis Imperfecta: Genetic evaluation**

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Osteogenesis imperfecta (OI) is a rare, hereditary bone dysplasia with a broad clinical spectrum that includes skeletal and extra-skeletal manifestations. It is genetically heterogeneous and there are multiple described mutations that explain the clinical variability of this entity and make it difficult to establish a genotype-phenotype correlation.

Objectives: To evaluate the clinical and genetic characteristics of the patient with OI.

Patients and Methods: Clinical and genetic descriptive study of a series of cases diagnosed of OI in a Pediatric Endocrinology unit in the last decade. Genetic study: The genes *COL1A1*, *COL1A2*, *CRTAP*, *FKBP10*, *LEPRE1*, *PPIB*, *SERPINF1*, *SERPINH1*, *SP7* were studied by sequencing NGS (SOLID 5500XL). Confirmation of the mutation by PCR amplification and subsequent sequencing.

Results: In the period studied, 6 patients (2 men and 4 girls) were diagnosed of OI with variable phenotype . The study of them and their respective families demonstrate the clinical and genetic heterogeneity characteristic of the disease. Case 1 presents a severe phenotype with numerous bone fractures and deformities. Case 2 is a mild form, with sensorineural deafness and without fractures. The remaining 4 cases are moderate intensity forms of the disease. In all cases, the clinical diagnosis was genetically confirmed, finding mutations in the *COL1A1* and *COL1A2* genes with AD inheritance and in one of the cases was *de novo* mutation. Three new mutations associated with OI have been described: c.1207G> T (p.Gly403Cys) in exon 22 of the *COL1A2* gene with AD inheritance (case 1). A duplication in heterozygosity of exons 1-49 *de novo* of the *COL1A1* gene (case 5). And, also for the first time, in exon 41 of *COL1A1* the mutation c.2938G> A (p.Gly980Ser) in case 6.

Conclusion: All patients studied with a variable phenotype of OI, as well as some members of their families, show genetic alterations in some of the genes related to this disease that confirm the

diagnosis. Our group have described for the first time three of the mutations : two in the *COL1A1* gene with moderate phenotype of the disease and another in *COL1A2*, in a patient with a severe OI phenotype.

Diabetes and Insulin

P2-62

The Effect of Carbohydrate Recognition and Counting Ability on Glycemic Control in Pediatric Patients with Type 1 Diabetes

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Many factors contribute to the glycemic control in pediatric patients with type 1 diabetes mellitus (T1DM). The purpose of this IRB approved study was to determine if there was a significant correlation between the ability of pediatric patients with T1DM to accurately recognize and count carbohydrates and their hemoglobin A1C (HgbA1C). T1DM patients aged 12-17 years completed the Koontz PedCarbQuiz (PCQ). Demographic and clinical data was extracted from the electronic health record. Subscales of Carb Recognition and Carb Counting were included from the Koontz PCQ. Spearman's correlation was conducted between HgbA1C, total PCQ score, Carb Recognition and Counting. Mann Whitney U test determined if there were differences between scores and insulin treatment. Significance was set at $p < 0.05$. The sample included 57 subjects with a median age of 14.5 (IQR 11.4, 17.2) years. The median BMI percentile was 72.3 (IQR 46.8, 93.5). About a third were categorized into the overweight and obese weight category (31%). Median HgbA1C was 9.2% (IQR 7.6, 10.4%). Subjects treated with insulin pump had a significantly higher total PCQ score compared to those treated with MDI. There was a negative and significant correlation between total PCQ score and HgbA1C ($\rho = -0.312$, $p = .037$) as well as Carb Recognition score (-0.297 , $p = .045$). Carbohydrate recognition knowledge was higher in subjects treated with insulin pump even though the actual difference in scores was not of practice significance. As carbohydrate knowledge increased, HgbA1C decreased. It is important to assess this knowledge to focus the education when working with pediatric patients.

P2-63

A Rare Case of Syndromic Diabetes due to an INSR pathogenic variant

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Introduction: The main type of diabetes seen in pediatric clinical practice is type 1 diabetes. Monogenic diabetes and syndromic diabetes are rare, but can be more common in areas where consanguinity is high.

A 12-year-old girl born to consanguineous parents who are first cousins, was referred after being diagnosed with diabetes and severe diabetic ketoacidosis. In addition, she had hypertrichosis, coarse facial features, acanthosis nigricans, a high arched palate, overcrowded teeth, short stature (height 134 cm /-2.4 SD) and a bone age of 9 years. Her tanner staging was B1P2A1. Her psychomotor development was normal.

Past medical history revealed bilateral oophorectomy at the age of 63 days. This was due to the presence of bilateral multiple ovarian cysts, diagnosed at the time as Juvenile Granulosa cell tumor.

Her initial investigations showed insulin resistant diabetes and growth hormone deficiency:

C peptide; 12.54 ng/ml (n: 1.1-4.4 ng/ml)
IGF1; 65 ng/ml (-2SD)

She is now on total daily dose of 84 U insulin (2.6 U/kg) and her HbA1c is 10%.

At the age of 13.9 years she was 139.5 cm (-3.1 SD) and her bone age was 10 years. Growth hormone stimulation was done with glucagon, showing growth hormone deficiency. Growth velocity was 4 cm/year. She was put on growth hormone and sex steroid replacement therapy.

Whole Exome Sequencing (WES) was carried out. Detected variants were filtered using bioinformatic software (Ingenuity and Varafit). She was found to be homozygous for a known pathogenic variant p.Thr937Met (c.2810C>T) in the *INSR* gene causing Rabson-Mendenhall syndrome her parents tested heterozygous for the same variant.

Conclusion: The incidence of Rabson-Mendenhall syndrome is estimated to be less than 1 in a million people. Insulin resistant diabetes mellitus, short stature, dysmorphic features, multiple ovarian cysts and hypogonadotropic hypogonadism have been described in these patients. In our case, the patient has hypergonadotropic hypogonadism due to a bilateral oophorectomy which may not have been indicated. Genetic testing in such cases of complicated diabetes with other phenotypic features could facilitate appropriate diagnosis and treatment.

The study relating to this case is funded by AZV grant number NV18-01-00078.

P2-64**Autoimmune thyroid diseases in children and adolescents with Maturity Onset Diabetes of the Young**

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Background and Aim: The relationship between T1DM and autoimmune thyreopathies is known and described, but the relationship between thyreopathies and other type of diabetes is not sufficiently clarified in pediatric age. The aim of our study was to assess the prevalence of autoimmune thyroid diseases (ATD) in children and adolescents with maturity onset diabetes of the young (MODY) in comparison with patients with T1DM and control group.

Patients and Methods: We examined 24 children and adolescents with MODY (11F/13M; 13.9±4.6 yr) and 166 patients with T1DM (80F/86M; 13.9±4.6 yr). The control group consisted of 62 age-matched healthy subjects (34F/28M). The diagnosis of ATD was based on autoantibodies examination (anti-TPO, anti-Tg, anti-TSHr), ultrasound picture and thyroid function test.

Results: ATD was diagnosed in 15 (10.5%; 9F/6M) patients with DMT1, in 5 (20.5%; 4F/1M) in MODY and finally in 1 control (1.6%). A significantly higher ATD prevalence was detected in T1DM and MODY compared to controls ($p=0.02$ and $p=0.001$, respectively), without difference between T1DM and in MODY ($p=0.15$). No difference was noted between genders in T1DM and MODY ($p=0.8$ and $p=0.008$, respectively).

Conclusion: Results show an increased prevalence of ATD in patients with MODY, as well as T1DM, resulting in recommendation of careful follow-up of all children and adolescents for presence of thyroid autoimmunity.

P2-65

Abstract withdrawn

P2-66**New mutation of the PDX-1 gene causes MODY Type 4 diabetes in a 17 year old girl with good response to oral antidiabetics**

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Background: Correct classification of diabetes mellitus in children and adolescents is essential for appropriate treatment.

Case Report: A 17 year old female adolescent was referred to our clinic due to hyperglycemia. She complained of dizziness and nausea. Her blood pressure was 160 /100 mmHg; she had hyperglycemia (208 mg/dl), a glycosuria and a ketonuria without ketoacidosis. Some members of the family were on insulin therapy and others were treated with oral antidiabetics. In our clinic we started an intensified therapy with basal and bolus insulin, to which the patient responded well. Insulin requirement was about 1 IU/kg body weight and the measured HbA1c 2 months afterwards was 6 %. The diabetes autoantibodies were negative. Taking the family history into consideration as well, we proceeded to a molecular examination of the MODY genes. Our patient had a mutation in the PDX-1 (Pancreatic and duodenal Homeobox 1) gene (c.479A>T p.(Glu160Val)). Mutations in the PDX-1 gene are responsible for MODY diabetes type 4. This mutation however has not yet been detected in other MODY diabetes patients. We switched the patient from insulin to oral antidiabetics with glibenclamid at a low dose of 0,875 mg once daily. The blood sugar levels remained in normal range and there were no side effects. Two months later the HbA1c was 6,0 %. Unfortunately, the other members of the family did not agree to a molecular examination.

Conclusion: We suggest that the detected mutation of the PDX-1 gene is the cause of the MODY diabetes in our patient. It is important to recognize MODY diabetes type 4 in children and adolescents, because this type of diabetes can be treated with oral antidiabetics instead of insulin.

P2-67**Periodontal disease among children and adolescents with Type 1 Diabetes Mellitus**

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Periodontal disease is defined as inflammation within the supporting tissues of the teeth, progressive attachment loss, and bone loss. It results from an extension of inflammation from the gingiva into deeper periodontal tissue. Periodontal disease is well studied among the adult population. Diabetes mellitus is considered as one of its risk factors among adults. We conducted this cross-sectional pilot study to investigate the association of periodontal disease and metabolic control among children with type one diabetes mellitus T1DM. We looked into the association between periodontitis and other variables including age, sex, BMI, duration of T1DM, number of DKA admissions, consumption of fizzy drinks, fruits and vegetables; as well as brushing of teeth and vitamin D status among children with T1DM. The study was conducted on children 6 – 14 years of age attending the diabetic clinic at KAH Alahsa, Saudi Arabia with specific inclusion and exclusion criteria were.

Patients were assessed by Pediatric endocrinologist at outpatients' clinic; and Pedodontists at the dental clinic who assessed them in 1-3 sessions using *Gingival Index scoring tool as well as Plaque Index score Pocket depths 'WHO'* periodontal examination probe.

Results: showed that out of 81 children enrolled in the study: 29 dropped off. There were 25 boys and 27 girls. 37% of the

52 children had moderate and severe gingival inflammations. 48% had sub-gingival plaque and calculus deposits. 29% had pocket depths greater than 3 mm. The gingival and plaque index scores were both moderately correlated with the HbA1c. The correlation of average HbA1c and GI Score after controlling for other variables was not statistically significant $p = 0.07$.

We concluded that: The findings of this pilot study indicate that children with T1DM have an actual gingival disease that predisposes them to future periodontitis. Dental examination, although it is not part of the standard care, it is important to take history and examine the mouth of children with T1DM by pediatricians and early referral to a dentist if concerned. Strict oral hygiene practices, and patient and family education are essential, which all could reverse the gingivitis and eliminate the risk of progressing to chronic periodontal disease. There is a gap of knowledge in this interesting research area. A large size-randomized controlled study is required to further elucidate the association between periodontal disease and metabolic control among children and adolescents with T1DM.

2h BG blood glucose of the abnormal blood glucose group was significantly higher than the normal group. The insulin secretion was increased, and the difference was statistically significant at 1h. The abnormal blood glucose in the non-secretion peak group accounted for 57.15%, and the abnormal blood glucose in the 2h secretion peak delay group accounted for 63.64%. In the abnormal blood glucose group, HOMA-IRI increased, HOMA-ISI and HOMA- β FI decreased with statistical difference.

5. SF and cardiac T2* had statistically significant differences

Conclusion:

1. The morbidity of diabetes was 14.77%, the morbidity of abnormal glucose metabolism was 30.68% in β -TM patients..

2. HbA1c can be used as an indicator to evaluate the average blood glucose level

3. Patients with β -TM showed impaired glucose tolerance, abnormal insulin secretion, impaired insulin secretion ..

4. When patients with cardiac iron deposition or SF > 4000ng/ml are more prone to abnormal glucose metabolism, and glucose metabolism indicators should be actively and closely monitored and iron removal therapy should be strengthened

P2-68

Pancreatic β Cell Function and its relationship with iron overload in Patients with β -Thalassemia Major

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Objective: The functional status and influencing factors of pancreatic beta cells in patients with β -thalassemia major (β -TM) were investigated .

Methods: A cross-sectional study was conducted in 88 patients with β -TM, with an average age of 11.3 ± 5.6 years. Thirty-two healthy subjects were selected as the control group. FBG, FINS, HOMA-IRI, HMOA-ISI and HOMA- β FI were calculated between the two groups. HbA1c, fructosamine and glycosylated albumin were detected in patients with β -TM, and oral glucose tolerance test, insulin release test, SF, cardiac and liver magnetic resonance T2* were detected.

Results:

1. FBG, FINS and HOMA-IRI increased significantly in the β -TM patients, whereas the HOMA-ISI and HOMA- FI decreased, but the differences of HOMA- FI were not statistically significant.

2. Among the 88 patients with β -TM, 13 (14.77%) patients had been diagnosed with diabetes, 27 (30.68%) patients had abnormal glucose metabolism, including 26 (29.55%) with impaired fasting glucose and 7 (7.95%) with impaired glucose tolerance. The youngest age of diabetes and impaired fasting glucose was 6 years old.

3. Patients with β -TM were divided into diabetes group, abnormal glucose metabolism group and normal glucose group, and the fructosamine (49 cases), glycosylated hemoglobin (54 cases) and glycosylated albumin (37 cases) were conducted. All the three indicators were increased with the aggravation of abnormal glucose metabolism.

4. Patients with β -TM were divided into the abnormal blood glucose group and the normal blood glucose group. The FBG and

P2-69

Gluten-free diet in children with recent onset type 1 diabetes is associated with slower pace of C-peptide decline, better metabolic control and lower insulin requirement at 12 months

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Objectives: Data on the role of gluten in type 1 diabetes (T1D) pathogenesis are scarce. We aimed to test whether gluten-free diet (GFD) can decelerate the decline in beta-cell capacity in newly diagnosed non-coeliac T1D children.

Methods: Forty six children (aged 10.2 ± 3.3 years) were recruited into this non-randomized self-selected intervention trial: 26 started with GFD, whereas 20 remained on standard diet. Main outcomes were the decline in C-peptide area under the curve (AUC) in mixed-meal tolerance tests and the differences in insulin dose, insulin dose adjusted A1c (IDAA1c) and HbA1c at 12 months. The adherence to GFD was tested by immunoreactive gluten in stool and food questionnaires at every visit. The quality of life (QoL) questionnaires were given to the patients and their parents at 12 months. Data were analyzed per protocol by linear and longitudinal regression models adjusted for sex, age and baseline HbA1c, insulin dose, C-peptide AUC and IDAA1c.

Results: A total of 39 patients (20 GFD group, 19 controls) were subject to final analysis. Immunoreactive gluten was found in the stool of 4 patients from the GFD group. The difference in trends of C-peptide decline between the groups was statistically significant at 32.6 pmol/L per month ($p=0.04$). The mean decrease in C-peptide AUC was 567 vs 919 pmol/L ($p=0.1$) at 12 months in GFD and control group, respectively. The GFD group had a lower insulin dose by 0.17 U/kg/day ($p=0.04$), lower IDAA1c by 1.51 ($p=0.006$) and lower mean HbA1c by 9 mmol/mol ($p=0.004$) at 12 months. There was no difference in daily carbohydrate intake between the groups ($p=0.83$). There was no statistically significant difference in QoL between the groups as reported by the patients nor their parents ($p=0.70$, $p=0.59$).

Conclusions: GFD kept over the first year after T1D diagnosis shows great promise as it was associated with lower C-peptide decline, lower insulin demand and HbA1c and more pronounced partial remission period.

P2-70

Evaluation of β -cell function in young MODY patients using a Mixed Meal Tolerance Test

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Background: Mixed meal tolerance test (MMTT) is a gold standard for evaluating β -cell function. There is limited data on MMTT and β -cell function in MODY patients.

Objective: The aim was to analyze plasma C-peptide (CP) levels during MMTT in MODY patients as a biomarker of β -cell function.

Methods: The cohort consisted of 39 patients with MODY genes mutations: 20 with GCK, 8 - HNF1A, 3 - HNF4A, 4 - KCNJ11, 2 - ABCC8, 1 - INS, 1 - KLF11. 59% were children (<18 years, n=23), and 41% - adults (18-27 years, n=16). The youngest patient with performed MMTT was 2.5 years old (KCNJ11).

MMTT was performed following standardized technique: after an overnight fast all patients ingested 6 mL/kg (maximum 360 mL) of standard liquid meal (1 kcal/mL). Blood samples for CP and glycemia levels were taken 10 min prior to the meal (t_{-10}), at the meal time (t_0), and time points: $t_{15}, t_{30}, t_{60}, t_{90}, t_{120}, t_{150}, t_{180}$. The results of CP were available at each time point for all subjects.

Area under the curve CP (AUC_{CP}), the baseline CP (CP_{base}), the peak CP (CP_{max}) concentrations were evaluated for all subjects and compared between MODY groups.

The cutoff of stimulated CP < 0.2 nmol/L was used in our study and described by other authors as a predictor of poor β -cell response and absolute insulin deficiency.

Results: The median of participants' age was 190 months [IQR 129]. The median of diabetes duration was 44 months [IQR 112]. The median of AUC_{CP} in the whole cohort was 162.7 nmol/L/180min [IQR 142.9], CP_{base} - 0.4 nmol/L [IQR 0.38], CP_{max} 1.28 nmol/L [IQR 1.28].

GCK diabetes patients had the best β -cell response, statistically significant differences of AUC_{CP}, CP_{base} and CP_{max} were found compared to HNF4A, KCNJ11 and KLF11 patients (p values <0.05).

HNF1A patients had significantly higher levels of AUC_{CP}, CP_{base} and CP_{max} compared to HNF4A and KCNJ11 patients (p values <0.05).

Six patients (3 HNF4A, 1 KCNJ11, 1 ABCC8, 1 KLF11) had all CP levels <0.2 nmol/L. These HNF4A, KCNJ11, ABCC8 patients had unsuccessful treatment change trial and they are all treated with insulin. Six HNF1A and 3 KCNJ11 patients had successful treatment change to oral sulfonylurea agents.

Conclusion: As expected GCK diabetes patients preserved the best β -cell function. A pretreatment challenge with MMTT might be a useful indicator to predict therapeutic success with oral sulfonylurea treatment after genetic diagnosis.

P2-71

The Effect of Different Forms of Maternal Dysglycemia on the occurrence of Neonatal Hypoglycemia in babies admitted to NICU

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We report the effect of different forms of dysglycemia on the occurrence of neonatal hypoglycemia in a large cohort of pregnant women studied as a part of a PEARL-Peristat Study, funded by QNRF- Doha-Qatar

Methods: Out of 12255 pregnant women screened during 2016-2017, 3027 women were identified with gestational diabetes (GDM) (WHO criteria) and 233 were diabetic (DM) before pregnancy. All dysglycemic women were managed according to related guideline/protocol with 3 or more clinical visits during the pregnancy period. Neonatal hypoglycemia was defined as a plasma glucose level of less than 30 mg/dL (1.65 mmol/L) in the first 24 hours of life and less than 45 mg/dL (2.5 mmol/L) thereafter. Data on neonatal hypoglycemia for babies admitted to NICU was collected from the hospital records.

Results: Babies born to DM and GDM mothers required more admissions to NICU for various reasons (24.5 %, 15.96% and 11.9 % respectively ($P < 0.01$)). Neonatal hypoglycemia in infants admitted to NICU occurred more frequently in babies of DM and GDM compared to non-diabetic women (45.6%, 18.6%, and 4.7% respectively). Neonatal hypoglycemia occurred more in babies < 36 weeks of gestational age (GA) versus those > 37 weeks of GA in non-diabetic women. However, neonatal hypoglycemia occurred more in babies born >37 weeks of age to DM (51.3%) and GDM (20.8%) when compared to babies born between 32 and 36 weeks of GA. Prolonged exposure to maternal Dysglycemia appears to stimulate more insulin secretion during in-utero life which is reflected more on the term and near-term infants.

Conclusion: Babies born to treated dysglycemic women are still prone to develop hypoglycemia more often than newborns of normoglycemic women. Full-term and near-term newborns delivered to mothers with treated dysglycemia had a higher prevalence of hypoglycemia compared to preterm newborns.

P2-72

Adropin, Afamin And Neudesin - Novel Biomarkers of Type 1 Diabetes Mellitus in Children

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Introduction: The incidence of type 1 diabetes mellitus (DM I) is rising. Newly discovered peptides: adropin, afamin and neudesin may play a key role in the diagnostic process in the future. Most studies assessing the relationship of those peptides provide data obtained from studies conducted on animals, adults with type DM II and women with gestational DM. There are only few studies concerning these relationships in children.

Aim of the study: The aim of the study was to evaluate the concentration of adropin, afamin and neudensin in blood serum of children with DM I and the control group, taking into consideration the duration of the disease.

Materials and Methods: The study population consisted of 138 patients aged 5-18 years (male: 40.58%). The examination was performed in the group of children with diabetes mellitus type I (n=68), and the control group (n=70). The diabetic group was divided into 4 subgroups: (I) newly diagnosed patients, (II) duration no longer than 5 years, (III) 5 to 10 years and (IV) > 10 years. Serum concentrations of all peptides were assessed and compared. P-value of 0.05 was considered statistically significant.

Results: Mean levels of adropin and afamin were statistically higher in subgroup III than in I: adropin (I 5978.18 vs III 10457.15 p=0.023), afamin (74.09 vs 95.72 p=0.037). Comparing subgroup I and IV there was the difference in adropin (5978.18 vs 9559.7 p=0.04). There was higher level of afamin in the subgroup II comparing to III (75.74 vs 95.72 p=0.018). There were statistically significant differences in peptides mentioned below and the control group: adropin, afamin and neudensin in the subgroup I, afamin and neudensin in subgroup II, adropin and afamin in subgroup III and afamin and neudensin in subgroup IV. The differences such as statistically significant increased mean level of adropin and afamin and stable mean level of neudensin correlated to longer duration of the disease were observed.

Conclusion: Our study shows that the concentration of adropin, afamin and neudesin may be connected with the duration of DM I and may change during the course of the disorder. That knowledge could be employed in the future to use these peptides as biomarkers of this disease. However further studies are needed.

P2-73

Prevalence, Time trend and predictors of Celiac Disease in Type 1 Diabetes

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Background: Celiac disease is an important association of type 1 diabetes with significant impact on growth and glycemic control. Identification of the disease in asymptomatic subjects highlights the need for celiac screening in type 1 diabetes. Disparity in screening guidelines suggests the need for exploration of time trend and predictors of the association.

Objective: To estimate the time trend, prevalence and predictors of celiac disease in children and adolescents with type 1 diabetes.

Methods: Time trend and predictors of celiac disease were studied in 203 children and adolescents with type 1 diabetes (105 boys) followed up for 4.8 (3.6) years with baseline and annual tissue transglutaminase (TTG) antibody levels in our Pediatric Endocrinology Clinic.

Results: Celiac disease was identified in 36 subjects (17.7%) during the course of study (3 before diagnosis, 19 at initial screening and 14 on follow-up). Twenty two subjects had elevated TTG at diagnosis of diabetes with biopsy proven disease in 19. Subjects with celiac disease at diagnosis had compromised growth reflected by lower weight standard deviation score [SDS -1.5 (1.4) as against -0.3 (1.1), P < 0.001] and BMI SDS [-0.9 (0.8) as against -0.1 (1.2), P = 0.009] than those without the disease. Celiac disease was identified in 14 subjects with normal initial TTG level after a mean follow up of 3.9 (2.9) years (range 1.5 to 12.6 years). Incident celiac disease was identified in 12 (85.7%) within five years of diabetes diagnosis and after 7 and 12 years in the remaining two. Subjects with incident celiac disease had compromised growth [weight SDS of -1.1 (-0.3) as against -0.3 (1.2), P = 0.03] and glycemic control [HbA1C of 11.8 (3.7) as against 9.5 (2), P = 0.003] than those without the disease. Importantly none of the subjects with incident celiac disease had gastrointestinal symptoms.

Conclusion: Celiac disease is common in type 1 diabetes with development of the disease usually within five years of diagnosis. Lack of gastrointestinal symptoms highlights the need for annual monitoring for the condition till at least five year of diagnosis.

P2-74

Impact of The Flash Glucose Monitoring System on Children With Type 1 Diabetes After The First Year of Using in Systematic Way

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The Flash glucose monitoring System(FGMS) is a system of measurement of the interstitial glucose levels in real time, safe,

effective and doesn't require calibration. Its low cost has allowed to be approved for all children under 18 years old by our Regional Health Service.

Objective: To assess the impact during this first year of use of FGMS in all children diagnosed with type 1 diabetes who previously used the classic method of capillary blood glucose. Every-body was trained in the use of this system.

Material and Methods: 80 children and adolescents participated in the study, assessing age, sex, age at diagnosis, duration of diabetes, insulin treatment they received, age at the onset of FGMS, pre-onset average HbA1c, HbA1c at onset and 3-6-12 months, number of blood glucose for verifying pathological values(Hypo-Hyper), registration of insulin doses and problems they could have with FGMS.

Results: 80 patients, 49%(39) males, mean age 13.55 ± 3.16 years(5.2-19), duration of diabetes 6 ± 3.99 years(1.4-13.9), middle ages at debut 7.5 ± 3.63 years(0.8-16), insulin treatment 70%(56) multiple doses, 16%(13) use subcutaneous catheters(Insuflon*, I-Port*), 14%(11) ISCI, age at the beginning of FGMS 12.28 ± 3.31 (3.8-18.4), mean HbA1c in the last year before to use of FGMS 7.58 ± 0.75 , HbA1c at baseline 7.66 ± 1 , HbA1c at 3 months 7.57 ± 0.9 , at 6 months 7.54 ± 0.8 , at 12 months 7.74 ± 0.8 , percentage of capillary glucose: didn't perform any 25%(20), occasionally(1-2/14 days) 31.2%(25) and sometimes (1-2 week) 21.3%(17) and always in situations of hyper/hypo 22.5%(18), in the last group included those are receiving treatment with ISCI. They wrote down doses of insulin 42.5%(34), didn't write anything 33.75%(27), occasionally 23.75% (19). Satisfaction state of FGMS is good 86.3%(69). They didn't have any problems with this method of control 82.5%(66), it took off before 14 days 15%(12), allergic reaction 1.25%(1), supply failure 1.25%(1). There hasn't been event of severe hypoglycemia.

Conclusions: The FGMS is a safe, effective and well-accepted method for the diabetic patient and the family, improving the quality of life of both, however the impact on the improvement of HbA1c was only observed in the first months because they got used to the comfort of the method and forgot blood glucose control recommended in extreme situations and therefore the results weren't as expected.

P2-75

Insulin treatment of Cystic Fibrosis Related Diabetes (CFRD) on BMI and respiratory function

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Cystic fibrosis related diabetes (CFRD) is one of the main complications of cystic fibrosis (CF), following inflammatory-degenerative damage of the pancreas. Aim of our study was to evaluate the effects of replacement insulin therapy in patients with cystic fibrosis complicated by overt diabetes or pre-diabetes on BMI and

respiratory function. We selected a sample of 17 insulin treated patients (Group T) and a sample of 17 controls with CF but normal glucose metabolism (Group C). Group T was in turn subdivided into overt diabetics patients and pre-diabetics patients (impaired glucose tolerance -IGT or indetermined glucose tolerance-INDET) on the basis of the glycated hemoglobin and OGTT. For each patients in Group T an observation period was established starting with the first insulin administration and ending after 12 months. For Group C patients, a compatible year of observation was chosen to compare with the year of study of the first sample. Data regarding Body Mass Index (BMI), Forced Vital Capacity (FVC), Forced Expiratory Volume (FEV1) and Peak Expiratory Flow (PEF) were collected at time 0, and at time 12. The number of respiratory infectious episodes during the year of observation and during the preceding year were recorded for Group T; the same parameters were studied in the two sub-groups. The results showed a significant increase in BMI in insulin treated patients compared to controls; this response was more satisfactory in the subgroup of overt diabetics. The study of spirometric parameters shows that in treated patients there was a significant improvement of PEF, the main effort-dependent respiratory index; this result was also more evident in the subgroup of overt diabetics compared to pre-diabetics patients. This data shows a positive impact of the insulin anabolic action on the development of the thoracic musculature and on the magnitude of expiratory effort. In contrast, the study of infectious episodes revealed a reduction of the number of episodes in treated patients more evident in those with pre-diabetes. Overall, our study makes us hypothesize the advantage of insulin treatment in CF patient in the early stages of glucose alteration (IGT, INDET).

P2-76

Coexistence of Medium chain acyl-CoA dehydrogenase deficiency (MCADD) and Type 1 diabetes (T1D): A management challenge

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Background: Medium chain acyl-CoA dehydrogenase deficiency (MCADD) is an autosomal recessive fatty acid β -oxidation defect. The enzyme is important in the breakdown of medium chain fats into acetyl-CoA to produce ketones, alternative energy source when glucose hepatic glycogen stores become depleted during prolonged fasting. In MCADD, during periods of fasting/ acute illness, there are insufficient ketones to compensate for the glucose energy deficit, resulting in a hypoketotic hypoglycaemia. The accumulation of toxic fatty acids can lead to encephalopathy and sudden death. Management includes avoiding prolonged periods of starvation, consuming high carbohydrate drinks during periods of illness and in symptomatic patients, reversal of catabolism and sustained anabolism by provision of simple carbohydrates by mouth or intravenously.

Coexistence of MCADD & T1D is rare and there is no causal association. A key goal of management in T1D is achievement of good glycaemic control to reduce risk of long-term complications.

This can in some cases increase the risk of hypoglycaemia which can be catastrophic in the presence of MCADD.

Case Presentation: We report our experience of 15-year old boy with both T1D & MCADD. He was diagnosed with MCADD at 16-months of age following an episode of diarrhoea and vomiting. He was managed with a frequent feeding regimen. His emergency regimen (during periods of illness) was high carbohydrate drink (SOS). He remained well until age 12 when he was diagnosed with T1D. This was managed with multiple daily injection therapy as he refused sensor augmented insulin pump therapy. The dose of insulin before his main meals was based on his insulin:carbohydrate ratio. In addition, he was allowed a free snack of 15g in between meals in-order to avoid long period of starvation. Should he want a snack more than 15g, we advised he gave insulin for it. Advice remained to continue to use his emergency regimen SOS 20 (which contains 40g carbohydrate) during acute illness. His blood glucose target was initially set at 5-9 mmol/l but this was later reduced to 4-7mmol/l. His HbA1c varied between 43mmol/mol (6.1%) and 66mmol/mol (8.1%). He has had no moderate or severe hypoglycaemia. His care was shared between the Diabetes team and inherited metabolic disease specialists.

Conclusion: Our case describes practical aspects of balancing the concurrent risk of hypoglycaemia whilst trying to achieve good glycaemic control, when T1D and MCADD coexist. Shared care between the specialist teams is vital to keeping the patients safe.

and 15 nutritionists. 35% had a good knowledge about physiopathology of T1D; definition of A1C were known by 23.8% but the A1C goal values were ignored by more than 40%, 63% knew injection sites even though 90% knew the need to injections rotation, 20% knew the hyperglycemia threshold and 54% practice a urinary test strip in case of hyperglycemia greater than 2.5g/L, 34% knew how to act correctly in case of hypoglycemia. Concerning the food knowledge: 63% said not to know food groups even though 76% knew the two kind of sugars (simple and complex); 89% said that fibers are necessary for diabetic children but 37% didn't know why and 34% didn't know where to find them. Only 22% knew the glycaemic index definition. Permitted food were correctly reported by 10.4% and restricted food were correct for 13%. Almost 90% said that sport is a key in the T1D management even though the mechanism was ignored by more than 58%. As far as the groups were concerned, we found the worst results among nurses and young doctors and best ones among nutritionists and paediatricians in trainee.

Conclusion: Education is known to be a key in the management of T1D in children. Educators are not always evaluated to assess the informations they spread. This study highlights the gap between what they should know and what they really know in a multicentric tunisian study. Our results emphasizes the need to develop training programs for health professionals to improve their basic knowledge of T1D.

P2-77

Education in type 1 diabetes mellitus (T1D): what do educators really know? A tunisian multicenter study among young doctors, nurses and nutritionists

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Background: Type1 diabetes mellitus is increasing worldwide in childhood. Education is an essential part of the package care at diagnosis. It addresses children with newly diagnosed type 1 diabetes and their families and is made by young doctors and paramedical staff (nurses and nutritionists).

Objective: to assess the knowledge of the medical and paramedical staff concerning the global management of type 1 diabetes in children.

Methods: Cross sectionnal survey from November 2017 to January 2018 from 6 pediatric centers (located in the main 3 tertiary care centers of the capital, Tunis) and one primary care center. We evaluated by a questionnaire first their **knowledge about diabetes**: physiopathology, symptoms, urine examination, A1C, injection sites, symptoms, causes and management of hyperglycemia and hypoglycemia and second their **food knowledge**: dietary effect on blood glucose, food group knowledge, adequate food consumption.

Results: 105 persons were recruited (38 nurses, 34 young doctors (6th and 7th year of medicine), 18 paediatricians in trainee

P2-78

A case of an infant with congenital hyperinsulinism complicated by diabetic ketoacidosis during treatment

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Background: Congenital hyperinsulinism (CHI) is a disorder causing persistent hypoglycemia due to oversecretion of insulin. Diazoxide, a K_{ATP} channel opener in pancreatic beta cells is the treatment of choice, however, the glucose level should be monitored carefully. We report here a case of an infant girl with CHI who was complicated by diabetic ketoacidosis (DKA) during acute febrile illness.

Case Report: A 15-month-old girl visited emergency room with recurrent seizures. She had a history of recurrent afebrile seizures since 4 months of age. She had no specific birth history or family history. On physical examination, her weight was 10.5kg (50-75 percentile) and height was 78.5cm (50-75 percentile). She also showed developmental delay, however, her tandem mass screening test, thyroid function test, and brain MRI were all normal. Hypoglycemia (serum glucose < 30 mg/dL) was noted, but serum insulin (8.36 μU/mL) and C-peptide (1.97 ng/mL) levels were inappropriately high. On glucagon stimulation test, blood glucose level increased from 38 mg/dL to 76 mg/dL, and serum insulin level was 7.6 and 4.4 μU/mL before and after glucagon stimulation, respectively. Abdominal ultrasonography was normal. Genetic study including ABCC8, KCNJ11, GLUD1, HNF4A, GCK, HADH, and UCP2 was all negative. Diazoxide (3mg/kg/day) was started under the diagnosis of CHI, and her self-monitored blood glucose level was well-controlled on follow up visit after discharge. However, after 4 weeks, she visited emergency center again with

2 days of fever and hyperglycemia. The serum glucose was 398 mg/dL with pH 7.293, HCO₃ 7.9 mmol/L, and positive serum ketone, which was consistent with DKA. Continuous intravenous insulin infusion was initiated with the rate of 0.05 IU/hr/kg. After recovery from DKA, her glucose level was well-controlled with the same dosage of diazoxide. She is 24 months old at present, and her developmental milestone has also been dramatically improved after diazoxide treatment.

P2-79

Clinical profile and follow-up analysis of Neonatal Diabetes Mellitus- single centre experience

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Aim: To study the clinical profile of Neonatal Diabetes Mellitus (NDM) at our centre

Objectives:

1. To study follow-up data on growth, glycemic control
2. To review genetic analysis

Introduction: NDM is rare and occurs at a frequency of 1:10,000. There is scarce literature on follow up of these patients although genetic data is well established (1). Developing country has its own challenge in the form of poor referral system, lack of reliable genetic labs as well as financial constraints necessitating SC Insulin injections over CSII by pumps. Our centre has an established genetic endocrine lab and is a referral centre for South India. We thus initiated this study to analyse data of our NDM cohort diagnosed in the last 10 years.

Results: Total of 9 patients had NDM (4 males). Median age at diagnosis was 72 days (14-180) with majority (6/9) being out-born. 7 were born at term gestation, median birth weight of our cohort was 2300 gm (900-2600). All were initiated on Insulin therapy and 2 required intravenous infusion at the outset. All had negative IA2 antibody, although 1 patient had a positive GAD. 1 patient got discharged against advice.

Follow-up data was available for 8 patients. The median follow-up age is 2.3 years (0.8-9.9). 5 are on basal-bolus and 3 on split-mix regime of Insulin with a mean dose of 0.85U/kg/d. The median HbA1c is 8.4 (6.6-9.5) at follow-up.

Growth shows improvement in both weight centile (from 2nd to 11.7th) and height centile (from 6.2nd to 14.7th) at follow-up.

7 underwent genetic testing (6- inhouse and 1- Exeter). 5/7 were born of consanguineous parentage. Mutation analysis was positive in 3/6 (1 each of EIF2AK3, INS, IL 2 RA)-2 of whom had consanguineous parents; negative in 3/6 and results are pending in 1 patient. Thus, our cohort demonstrated a 50% positive rate for genetic mutations and none with the common K-channel mutation. In all of them siblings were unaffected. All 8 patients are alive and 1 with IL2RA is being worked up for HSCT.

Conclusion: Our study demonstrates that there is good chance of survival and improvement in growth with Insulin therapy among patients with NDM. There is 50% genetic mutation positive

rate in our cohort. Interestingly 1 patient with IL2RA mutation also had GAD positive status and apart from Insulin therapy will need HSCT.

Reference

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P2-80

Effect of multiple dose insulin on glycaemic control and adiposity in children and adolescents with type 1 diabetes; a Sri Lankan experience

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Objective: To describe the glycaemic control and change in body mass index (BMI) in children and adolescents with type 1 diabetes (T1DM) after converting to multiple dose insulin regime (MDI) from fixed dose insulin regime (FD).

Methods: A retrospective observational study on children with T1DM who were converted to MDI from FD at the Lady Ridgeway Hospital from January 2013 to June 2018. Mean haemoglobin A_{1c}(HbA_{1c}) was compared at the initiation of MDI, after 6 months, after 1 year and in January 2019. Change in adiposity was measured by BMI standard deviation scores (BMI SDS) which was compared at the initiation of MDI and in January 2019.

Results: Forty-five (19 male) children who were converted to MDI were studied. Mean ages at initiation and in January 2019 were 10.5 years (range 3.5 to 14.3) and 14.3 years (range 8 to 18) respectively. The follow up period varied from 6 months to 4 years and nine months. Mean HbA1C at initiation (9.6%) had decreased to 8.4% (p<0.01), 8.3% (p<0.001) and 8.7% (p<0.01) at 6 months, at 1 year and in January 2019 respectively. All HbA1C changes were statistically significant. The difference in BMI SDSs at initiation and in January 2019 was not statistically significant (p=0.076).

Conclusions: A significant improvement in glycaemic control was seen 6 months after converting to multiple daily insulin regime, and the improvement was sustained even after a mean duration of 3.5 years. Significant change in adiposity following initiation of MDI was not observed.

P2-81

A de novo pathogenic heterozygous mutation of the insulin receptor gene in a patient with type A insulin resistance syndrome

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Background: Defects of the insulin receptor gene (INSR) can cause genetic syndromes associated with a wide diverse range of

congenital insulin resistance from milder insulin-resistant diabetes mellitus (Type A insulin resistance syndrome, TAIRS) to leprechaunism (Donahue syndrome). Clinical features in TAIRS vary due to the severity of damage in *INSR*, precise diagnosis is challenging.

Materials and Methods: We investigated a nearly 15-year-old adolescent girl who initially diagnosed as non-classical congenital adrenal hyperplasia (CAH) outside. Clinical features and biochemical data of this patient were analyzed comprehensively at first in our hospital. Then, the whole-exome sequencing were performed by Next-generation sequencing technology and was further validated by Sanger sequencing. The functional damage of this mutation in *INSR* was predicted by the silico analysis and confirmed by vitro functional analysis eventually.

Results: The adolescent patient came with chief complaints of delayed menarche and hirsutism. She was not obese (BMI 17.3 kg/m²), but had hirsutism, acanthosis nigricans with a high homeostasis model assessment of insulin resistance (HOMA-IR) score of 25.0 indicated severe insulin resistance. She was clinically highly suspected of Type A insulin resistance syndrome. A heterozygous mutation c.3814T>C (p.Cys1272Arg) was detected in *INSR* of the patient and was further validated by Sanger sequencing, while there was no mutation detected at the same site of *INSR* in her parents. The silico analysis with Polyphen-2 and PROVEAN software showed "probably damaging" and "deleterious" respectively. The mutation in *INSR* reduced the expression of insulin receptor precursor protein and mature insulin receptor protein, and decreased the phosphorylation levels of AKT in the insulin receptor signal transduction pathway. Immunofluorescence also indicated the lower expression of insulin receptor on the CHO-k1 cell membrane transfected with the mutant *INSR* than that with the wild type *INSR*, which contributed to the effects to the function of the insulin receptor.

Conclusion: The heterozygous missense mutation of exon 22 of the *INSR* gene (c.3814T>C) is a new type of mutation in TAIRS, which is first reported at home and abroad. Patients with TAIRS are easily misdiagnosed as non-classical CAH in the clinic. Those adolescent female patients with severe insulin resistance, hyperandrogenism and acanthosis, should be highly alert to TAIRS. Genetic screening can help improve the early diagnosis of TAIRS.

Keywords: insulin resistance, acanthosis nigricans, insulin receptor (*INSR*) gene, mutation, Type A insulin resistance

P2-82

Thiamine responsive megaloblastic anemia syndrome with restrictive cardiomyopathy: a case report

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Background: Thiamine-responsive megaloblastic anemia syndrome (TRMA), also known as Rogers syndrome, is characterized by megaloblastic anemia, sensorineural hearing loss, and diabetes mellitus. Disturbances of the thiamine transport into the cells results from homozygous mutation in the *SLC19A2* gene. Rhythm disturbances and structural cardiac anomalies have been described in the syndrome.

Case Presentation: We report a boy who presented with sensorineural deafness, neonatal diabetes, macrocytic anemia since the age of 6 months. He received frequent blood transfusion and was treated with insulin 2 IU/kg/day without achievement of good glycemic control. At the age of 7 years, he presented hepatomegaly with mild elevation of liver enzymes. His chest x-rays showed cardiomegaly, ECG showed accelerated junctional rhythm and ECHO revealed restrictive cardiomyopathy with mild tricuspid regurge and mitral regurge. On doing genetic testing, he was found to be homozygous for an *SLC19A2* nonsense mutation, p.Trp387Ter. He started treatment with thiamine 100 mg/day which increased up to 200 mg/day with improvement of hemoglobin level and decrement of insulin requirements. Low dose diuretics were started for his cardiac condition.

Conclusion: Patients with megaloblastic anemia, sensorineural hearing loss, and diabetes mellitus should undergo genetic testing for *SLC19A2* mutations. Thiamine therapy should be considered in cases of TRMA and the dose of thiamine therapy may be increased according to the clinical response. To our knowledge, this is the first case of TRMA reported to have restrictive cardiomyopathy.

P2-83

17q12 Deletion and a Family History of Diabetes

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Introduction: 17q12 deletion syndrome is associated with an enlarging phenotype, the most frequent clinical findings being renal and genitourinary malformations, diabetes mellitus (β -cell developmental defect) and exocrine pancreas deficiency, variable cognitive impairment with dysmorphic features.

Diabetes, known as MODY 5 (maturity-onset diabetes of the young), is an autosomal dominant monogenic type and the most commonly identified mutation is an entire *HNF1B* gene deletion.

Many patients experience progressive deterioration of glucose homeostasis over time. Metformin could be the first-line drug, but early insulin therapy is required.

We present 2 brothers with maternally inherited 17q12 deletion including *HNF1B*.

Case presentation: At the age of 18 years, the patients' mother was diagnosed with type 1 diabetes (T1DM). By the age of 33, she had given birth to 3 dysmorphic children. The genetic analysis of the mother and children found a 1.4-Mb deletion in chromosome 17q12, including the *HNF1B* gene.

Patient 1 is an 11-year-old male child who presented with polyuria. His medical history included cognitive delay, hepatic cytolysis, and ophthalmic abnormalities with normal brain magnetic resonance imaging. He was overweight, with mild cognitive impairment, behavioral difficulties and dysmorphic features. The biological check-up revealed: hyperglycemia, glycosuria, without ketonuria, HbA1c 7%, preserved insulin secretion and negative autoimmune markers of T1DM. He also presented mild hyperuricemia and hepatic cytolysis. There were no renal or genitourinary abnormalities.

With a MODY 5/17q12 syndrome diagnosis, metformin was started with immediate good glycemic control. Fifteen months later, he developed a severe keto-acidosis and the treatment was changed; currently, he is under insulin 1.07 u/kg/d.

Patient 2 is a 14-year-old male child who presented with the same phenotypic and genotypic features as his younger brother. At diagnosis, he was asymptomatic, but obese.

His biological check-up revealed fasting glycaemia, HbA1c 6.8%, preserved insulin secretion, normal hepatic and renal function. He had no renal morphological abnormalities. Metformin was started; twelve months later, his HbA1c was 11.6%, and he had lost 4 kg. He is currently receiving insulin 0.32 u/kg/d.

Conclusion: MODY 5 diabetes treatment remains challenging.

Our cases showed similar phenotypes, with some biochemical differences. Their evolution was marked by early insulin requirement, maybe in a context of aggravating obesity, and different response to insulin therapy.

P2-84

An Unusual Presentation of Type 1 Diabetes

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Introduction: Hyperglycemic hyperosmolar state (HHS) and diabetic ketoacidosis (DKA) are life-threatening emergencies in diabetic patients. While DKA at presentation of T1D in children represents about 25% of cases, HHS is very unusual as a first presentation.

Case: A 10 year old Haitian-Sudanese boy presented to our ER for obtundation. He had a 10 day history of polydipsia and polyuria followed later by vomiting, for which he drank mainly juice and soft drinks. On the day of presentation, he had difficulty rousing. In ER, he was tachycardic and hypotensive with a GCS of 8. Initial labs showed pH 7.1, bicarb 9.2, glucose 130mmol/l, Na 125mmol/l, K 4.0mmol/l, creatinine 352umol/l, urea 25.2mmol/l, and mild ketonuria. He was started on our DKA protocol after receiving three fluid blouses for hypovolemic shock. Urgent CT and MRI head were normal. The patient was admitted to ICU for management of profound dehydration, requiring intubation and inotropes. HbA1c was found to be 11%. Repeat MRI brain on day 3 due to agitation revealed a superior sagittal and straight sinus thrombosis. Other complications during his hospitalization included unilateral vocal cord paralysis without a clear etiology and non-pressure ulcers over the ischia region and in the left gluteal fold. The patient was admitted for 34 days, the latter weeks dedicated mainly to wound care. He was discharged with only a residual vocal cord paralysis but a grossly normal neurological exam. His BG were well controlled on 1.2unit/kg/day of insulin.

Discussion: The classic presentation of HHS in children is usually in obese adolescents with T2D. The symptoms tend to occur more gradually, and the mortality rate from HHS is higher than that from DKA. Their fluid deficit is estimated to be double that associated with DKA alone, and as such tends to be grossly underestimated, especially by treating physicians who rarely encounter this condition. Our patient presented with both HHS

and mild DKA and fortunately survived with few sequelae. At follow-up he had progressed to have remission (honeymoon period) lasting five months and continues to have well-controlled diabetes with the most recent HbA1c of 7.1% on 0.75unit/kg/day of insulin.

P2-85

Clinical characteristics and treatment outcomes in patients with autoantibody-negative ketosis-prone diabetes

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Objective: Ketosis-prone diabetes (KPD), characterized by presentation with diabetic ketoacidosis (DKA) in patients lacking the typical features of autoimmune type 1 diabetes, is a heterogeneous syndrome. The objective of this study is to ascertain the presence of A-β+ (autoantibody-negative, β-cell functional reserve) KPD in Korean children and adolescents and to study their characteristics in this group. Method: Diabetes patients (n = 9) with suspected KPD (A-β+) were studied over a period of 1 year with evaluation of clinical and biochemical characteristics. These were compared with a control group (n = 34) of KPD (A+β-). Preserved β-cell function after the index DKA was defined as fasting insulin serum C-peptide level > 1 ng/mL.

Results: A-β+ KPD patients had a greater mean BMI and higher frequency of obesity, significantly older age than the A-β- KPD. On serial follow-up, the patients with A-β+ KPD achieved recovery of their beta-cell function.

Conclusions: This is the first study to report of A-β+ KPD in Korean children and adolescents with evaluation of natural course of their diabetes. Our data showed that 9 out of the 49 patients who were admitted with DKA at diagnosis for diabetes characteristics of A-β+ KPD which suggested a prevalence rate of 18.4%.

P2-86

Factors influencing the formation and support of the motivation to self-control of adolescents with type I diabetes mellitus

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Background: Indicators of Type 1 diabetes mellitus in children and adolescents in Ukraine have increased in recent years. The effectiveness of treatment of this disease depends not only on the level of medical support of the patient, but also on the training of patients in the principles of managing their own illness. Low motivation of patients for treatment and control of illness, refusal to bear responsibility for their state of health and well-being can significantly affect the outcome of treatment.

Objective and Hypotheses: the purpose of our study was to determine the factors that influence the formation and support of self-control motivation in adolescents with diabetes type I.

Method: We examined 60 adolescents with type I diabetes at the age of 12-18, 32 of them are girls and 28 are boys.

Results: According to the results of testing, it was established that the majority of adolescents have a high level of compliance (75%), behavior change (82.5%) and achievement of symptomatic improvement (82.5%). For adolescents with a high level of HbA1 and poor compensation, there are guidelines for obtaining a secondary benefit or motivation for taking a passive position. 17.5% of adolescents were categorically determined that parents and doctors should be more active than adolescents themselves in the fight against adolescent diabetes. 37.5% of adolescents expect to receive a second benefit from the fact that they are suffering from diabetes. It allows us to suppose that there is a hidden manipulation in their behavior arsenal.

As a result of the factorization of the obtained data, a factor matrix was determined, which explains 73.4% of the dispersion. There were established 6 factors influencing the formation and support of motivation to self-control in adolescents: patient's compliance, locus-control of health, personality traits (anxiety, infantilism, low self-esteem, self-doubt), behavioral features (impulsivity, frustration, behavior strategies in a disease situation, a life perspective (the idea of own future), intelligence (understanding of causal relationships).

Conclusion: The obtained results are the basis of the author's "Questionnaire for studying the motivation of ill adolescents for the treatment of diabetes", the application of which will contribute to a more detailed study of the characteristic of the patient units before the treatment of type I diabetes mellitus.

P2-87

Glycemic Control in Egyptian Adolescent Girls with Type 1 DM

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Background: Adolescents with Type 1 Diabetes (T1D) have worse metabolic control than preadolescent children due to poor adherence with medications and insulin resistance related to puberty hormones. Adolescent girls are at a particular risk for poor control as insulin sensitivity decreases in the luteal phase and menstrual cycle. Progesterone, secreted in the second half of the cycle, may cause an increase in appetite and caloric intake.

Objectives: This study was conducted to assess the effect of puberty on the glycemic control of adolescent type 1 diabetic females following up in Diabetes, Endocrine and Metabolism Pediatric Unit (DEMPU) of the Children's Hospital of Cairo University and to study the effect of menstruation on insulin demand and blood glucose control in these girls.

Patients and Methods: A cross-sectional study on thirty pubertal adolescent girls (group 3), thirty prepubertal girls (group 1) and thirty boys in variable stages of puberty (Group 2-Tanner stages 2-5) all with ages ranging from 10-15 years and similar mean T1D duration (5.12-5.42 years). We compared mean blood glucose levels, mean insulin doses and mean HbA1Cs (average of the last 4). In Addition, group 3 patients were asked to keep tight records of their blood glucose one week before and during the week of menstruation and to increase their insulin doses to correct for any high blood sugars as needed. We also compared the degree in the participation in sports, psychological issues in the three groups.

Results: Mean blood glucose levels were higher in pubertal girls than in both other groups reflected also in their mean HbA1Cs and insulin requirements ($p<0.05$). A third of pubertal girls did not participate in any form of walking or sports compared to 13.3% of pubertal boys and 20% of pubertal girls. The difference was highly significant ($p<0.001$). Anorexia and dissatisfaction of body image was non significantly more in pubertal girls. Fears from not finding a spouse were significantly higher in pubertal girls ($p=0.4$). About half of the adolescent girls haven't told their friends about their diabetes ($p<0.001$)

Conclusion: Puberty and menstruation in T1D girls have an adverse effect on diabetes control. Closer monitoring is needed during the menstrual cycle. Higher HbA1C levels may also be related to lower participation in sports in this group which is common in Arab countries. Sports should be encouraged in this group. Psychological care should be specially addressed to this vulnerable group.

A qualitative study investigating the experiences of using Solution Focused Therapy in a paediatrics diabetes team

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Introduction: It is essential that children and young people with diabetes are supported to manage their diabetes effectively to prevent the development of early complications, by education and self-management aimed towards maintaining good glycaemic control. However, the common clinical challenge is difficulty in engaging adolescents and young people with poor glycemic control in their diabetes management.

Solution Focus Therapy (SFT) has been found to be especially beneficial with children, adolescents and teenagers because it is a brief model translated to all age groups (Franklin et al, 2007; Kim & Franklin, 2009).

With this in mind, it is of interest to discover the attitudes, experiences and common themes a paediatric diabetes team shares whilst using SFT and how it impacts on their delivery of care. Currently there has been no research to evaluate any diabetes team's involvement with clinical health psychology. This qualitative study aims to evaluate the diabetes team's experiences from using SFT in their deliver of diabetes care, discovering aspects that assist their work and providing a greater insight into the use of SFT in a paediatric diabetes setting.

Methodology: The study had a qualitative descriptive design which was considered the best method for describing the team's experiences with SFT (Polit and Beck, 2012).

Data was collected using semi-structured interviews within a specialist paediatrics diabetes team in the North West of England. The team consists of a Consultant Paediatrician, 2 specialist nurses, 1 patient educator and a specialist dietitian.

Face-to-face, semi structured interviews were conducted individually with each member. One independent researcher completed all interviews. Voice-recorded interviews were transcribed verbatim and analysed by another independent researcher using a thematic approach to identify main themes.

Results: It was found that SFT used within the team, improved self-reported confidence, skill, trust and relationships with patients and their families. Additionally, each team member reflected how patient and their families have responded positively to the SFT approach. SFT was also reported to be a strategy that improves diabetes management and facilitates a trusting relationship between clinician and patient which is person centred.

Conclusion: Evaluating staff experiences of utilising SFT in the delivery of paediatric diabetes care highlighted that a team's approach to SFT is perceived to facilitate and support children, young people and their families in managing diabetes. The implications of SFT for clinical practice and the dissemination of this approach to routine clinical practice should be explored.

The Prevalence of Chronic Kidney Disease in Children and Adolescents with Type 1 Diabetes Mellitus in The Republic of Uzbekistan

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Chronic kidney disease (CKD) is one of the most significant medical and socio-economic problems of our time.

Purpose of the research: To study the prevalence of chronic kidney disease in children and adolescents with type 1 diabetes in Uzbekistan.

Materials and Methods: For conducting epidemiological studies there were examined children and adolescents of type 1 diabetes. Epidemiological data were studied on the basis of the developed protocols, filled in with children and adolescents of type 1 diabetes consisting in the dispensary registration in the specified areas.

Results and discussion: The study of gender differences in the group of children and adolescents in type 1 diabetes revealed the prevalence of females in both 41.5 / 58.5% (n = 139/196) and adolescents 49.4 / 50, 6% (n = 128/131) groups. The majority of children with type 1 diabetes 80.6% in the surveyed regions were without CKD, 7.5% were in stage I of CKD; 6.6% in stage II CKD; 4.2% for III and 1.2% for Stage IV CKD. Among children with CKD (n = 65), the majority were mainly in stages I and II of CKD. In the Republic of Karakalpakstan and Surkhandarya regions among the examined children of type 1 DM, there were no cases of III and IV stages of CKD. However, IV stage of CKD was detected in the 1st child in the Khorezm region and in 3 children in the city of Tashkent. Thus, the majority of children with type 1 diabetes in the surveyed regions were in stages I and II of CKD. The majority of adolescents with type 1 diabetes 64.5% in the surveyed regions were without CKD, 17.0% were in stage I of CKD; 8.1% in stage II CKD; 4.6% for III and 5.8% for Stage IV CKD. Among the examined adolescents with type 1 diabetes, CKD stage V was not detected. Thus, the majority of the examined adolescents with type 1 diabetes in the regions were at stage I and II of CKD.

Conclusion: It is established that the actual prevalence of CKD : in children, 19.4% and in adolescents, 35.5%. Among children and adolescents with type 1 diabetes with the presence of CKD, most were in stage I and II of CKD. However, predominance of females among both 41.5 / 58.5% of children and 49.4 / 50.6% among adolescents, which plays an important role in the formation of risk groups for further research.

Neonatal Diabetes in Two Siblings with FOXP3 Variant

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Background: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare disorder caused by loss-of-function mutations in the gene encoding the forkhead box P3 (FOXP3) transcription factor. This factor plays a key role in the differentiation and function of CD4+ CD25+ regulatory T cells, essential for the establishment and maintenance of natural tolerance.

Objective: To describe clinical, biochemical and genetic characteristics in two siblings with neonatal diabetes and a novel FOXP3 mutation.

Method: Genomic DNAs were extracted from peripheral blood leukocytes from both patients and their parents with informed consent for genetic studies. Sanger sequencing.

Results: Patient 1: male, born at term, birth weight 3,050 kg. Neonatal diabetes diagnosed with DKA at 1 month old. Glycemia 5,11 g/L. HbA1c 4%. C-peptide 0,1 ng/mL. Anti-insulin Antibodies 13,4 U/mL. Ig E 7710 IU/mL. Treatment with NPH and aspartic insulin led to variable glycemic control. Enteropathy with severe and persistent diarrhea was confirmed by endoscopy and biopsy and required exclusive parenteral nutrition. IPEX syndrome was suspected based on neonatal diabetes, enteropathy and eczema. Multiple infectious diseases associated with autoimmune cytopenias. Died cachectic at 6 months old because of sepsis after 5 months at hospital. Sequence analysis confirmed he was hemizygous for a novel FOXP3 frameshift variant resulting in loss of the stop codon, p.(Thr428fs). Evidence up to that moment suggested that the variant was likely pathogenic, consistent with IPEX syndrome. His mother is heterozygous for the mentioned variant, being a carrier.

Patient 2: male, born at term, birth weight 1,720 kg. Given his older brother's record, patient 2's glycemia was controlled since birth. He showed hyperglycemia 6 hours after he was born. Glycemia 2,5 g/L. HbA1c 4%. C-peptide 0,1 ng/mL. GADA 11,1 U/mL. IgE 2,3 IU/mL. Insulin requirement since his first day of life. He received aspartic, glargin and finally lispro administered by insulin pump. Variable glycemic control. He has received hydrolyzed formula since birth. Hospital discharge at 43 days of life. No persistent enteral symptoms at present (3 months old). He underwent a Rotavirus infection requiring a short hospitalization. Adequate weight gain. His genetic testing showed patient 1's same variant. He is close to receive bone marrow transplant.

Conclusion: Distinctive manifestations have been described in two siblings with neonatal diabetes as first diagnosis with a novel variant in FOXP3's Sanger sequence. Their mother is the carrier of the X-linked mutation.

A novel variant of the WFS1 gene with dominant inheritance causing Wolfram-like syndrome

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Aims/hypothesis: The Wolfram syndrome, also known as the DIDMOAD syndrome (Diabetes Insipidus, early-onset Diabetes Mellitus, progressive Optic Atrophy, and Deafness), is mostly associated with recessive mutations in the *WFS1* gene. However, dominant mutations in the *WFS1* gene were described as causing less severe Wolfram-like syndrome, or isolated optic atrophy, or low-frequency sensorineural hearing loss.

Methods: Here we describe a patient, currently an 20-years old boy, with congenital hearing loss (received cochlear implant in 2.5 years of age), bilateral cataracts, epilepsy, autism, and non-autoimmune insulin-dependent diabetes mellitus diagnosed at 8 years of age. His father is reported as healthy; mother has an undefined hearing impairment, and she underwent an unspecified eye surgery and wears glasses. Genetic testing included Sanger sequencing of the *WFS1* gene (promoter region and all 8 exons with exon/intron boundaries) and MLPA (SALSA P163-GJB-WFS1, MRC-Holland) for identifying potential deletions or duplications. All tests were performed in the patient and his parents.

Results: A novel heterozygous in-frame deletion NM_006005.3:c.2608_2619del, p.(870_873del) was identified in the exon 8 of the *WFS1* gene in the patient DNA. This variant was not found in the mother. No other rare variant was found by sequencing and no dosage defect was detected using MLPA in both the patient and his mother. No *WFS1* mutations were found in his father.

Conclusions/interpretation: The identification of this novel heterozygous variant found in the patient supports the diagnosis of the Wolfram-like syndrome with dominant inheritance in the patient. However, the suspicious phenotype of the mother keep a possibility of a second, yet unidentified, genetic defect open. Variable inheritance pattern together with the progressive character of clinical symptoms complicate the diagnosis and family genetic counseling in Wolfram syndrome.

P2-92**An Impaired Lipid Profile is a Sign of Reduced Insulin Sensitivity in Children and Adolescents at Type 1 Diabetes Onset**

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At type 1 diabetes (T1D) onset, international guidelines recommend a starting subcutaneous insulin dose widely ranging from 0,5 to 1 u/kg/day. In fact, many factors such as age, pubertal stage and the severity of ketoacidosis, may influence insulin sensitivity. However, it is a common experience that many subjects may require a higher insulin daily dose than expected, with the subsequent need of longer time to achieve stable blood glucose values and the extension of days of hospitalization. The aim of this study was to find possible predictive factors related to insulin total daily dose at T1D onset. This is a retrospective study of 95 consecutive subjects at T1D onset, occurred between April 2014 and March 2018. Clinical and laboratory data were analyzed. Insulin requirement was expressed as the maximum amount of insulin administered subcutaneously during hospitalization per kg in 24 hours. Parameters analyzed are showed in table. Insulin requirement was strongly correlated to lipid assessment, in particular to triglyceridemia ($p=0.0001$). Though, as already reported, the severity of ketoacidosis and HbA1c at onset negatively affected insulin sensitivity ($p<0,015$), at multiple regression the significant variable was triglyceremia. As expected, the duration of hospitalization increased proportionally to the units of insulin/kg ($p=0.0013$). At 12 months after diagnosis, the average insulin dose was directly related to that at the onset, both in the total sample of subjects ($p=0.0006$) and in the subsample with HbA1c at 12 months <54 mmol/mol ($p=0.0001$). No correlation with symptoms duration and reported weight loss. Conclusions: triglyceridemia at the diagnosis of T1D is suggestive of increased insulin requirement, regardless of the severity of the acidosis. This could potentially reduce the time to reach stable blood glucose values and decrease the days and costs of hospitalization.

Mean age (yrs)	8,7 ± 4,4
HbA1c (mmol/mol)	103 ± 27
First blood glucose value (mg/dl)	481 ± 295
Total Cholesterol (mg/dl)	188,8 ± 55,6
HDL cholesterol (mg/dl)	45,5 ± 15,3
Triglycerides (mg/dl)	225,7 ± 242,0
Symptoms duration (days)	38 ± 49
Hospitalization duration (days)	9,4 ± 3,4
Intravenous Hydration duration (hours)	18,0 ± 25,3
PH	7,3 ± 0,1
HCO3 (mmol/L)	18,8 ± 7,6
Weight loss reported (kg)	2,4 ± 2,5
C-peptide at onset (ng/ml)	0,018 ± 0,01
Insulin requirement at onset (U/kg/day)	0,96 ± 0,45
Insulin requirement at 12 months (U/kg/day)	0,58 ± 0,23

P2-93**The growth hormone treatment and carbohydrate metabolism in children born small for gestational age**

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Background: Children who were born small for gestational age (SGA) or with intrauterine growth restriction (IUGR) have increased risk of metabolic disorders such as insulin resistance, diabetes mellitus type 2 and coronary disease in adulthood. Most of those children after catch-up growth achieve the same growth as their peers. Nevertheless 10% of them persist finally short as adults. In the last decade some countries introduced the rhGH treatment to improve the final height in this children. The interest is whether the rhGH treatment gives this patient additional metabolic advantages.

Aim of study: The aim of study was to analyze carbohydrate metabolism parameters in SGA children before and in the course of rhGH treatment.

Material and Methods: We analyzed medical records of 86 pediatric patients, which 41 were SGA children with normal GH secretion and 45 children with growth hormone deficiency (GHD).

We used the data taken before the treatment with rhGH from both groups and we compared them with each other. We used following parameters: fasting glucose, fasting insulin, HbA1c levels and HOMA-IR, QUICKI indexes.

In SGA group we used data before and after one year of treatment with rhGH. We compare the same parameters as before the treatment and additionally glucose and insulin levels after 2 hours of oral glucose tolerance test.

Results: In our study there were no significant differences in fasting glucose, fasting insulin, HbA1c value and HOMA-IR, QUICKI indexes between both groups before growth hormone treatment.

After 1 year of treatment in the SGA/IUGR patients there was statistically significant difference in insulin level in 120 min OGTT ($p=0,03$).

No significant difference was found in fasting glucose, glucose in 120 min of OGTT, fasting insulin, insulin in 120 min of OGTT, HOMA-IR, QUICKI. One patient fulfilled the criteria of impaired glucose tolerance (IGT).

Conclusions: Statistically significant higher concentration of insulin in OGTT in SGA children during rhGH treatment may suggest that in these patients, growth promoting therapy does not provide parallel metabolic benefits.

Key words: Fasting insulin, fasting glycemia, insulin resistance, HOMA-IR, QUICKI, SGA

P2-94**Empirical sulphonyurea in Neonatal diabetes: results from a Tertiary care centre**

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Background: To study the genetic profile of infants with neonatal diabetes (NDM) and response to empirical glibenclamide.

Method: A retrospective study between 2014-2018, the data retrieved from patients admitted with neonatal diabetes with genetic analysis. Started on insulin and empirical glibenclamide given in selected cases to evaluate the effects. Glibenclamide was started in 4 children who were not euglycemic on insulin, and had no syndromic features, non consanguineous parents.

Results: 11 children were diagnosed with NDM and genetic testing were done in all. 2 cases were KCJN11, one was HNF1B, one INS, one FOXP3, one EIF2AK3. 4 cases were started on oral glibenclamide and 3 responded well. No adverse events were noted in any of the infants.

Conclusion: glibenclamide is a safe drug for treating neonatal diabetes, and may be empirically tried in selected cases while awaiting the genetic results.

P2-95**Diabetes Mellitus, Severe Acanthosis Nigricans and Short Stature: a Rare Association in Chinese Children**

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Objectives: To report a case of concomitance of diabetes mellitus, severe acanthosis nigricans, short stature in a 6-year boy.

Methods: Retrospective review of medical records of a patient with diabetes, acanthosis nigricans and short stature followed at the Departments of Endocrinology and Metabolism, Children's Hospital of Fudan University. This rare case was undergoing whole exome sequencing.

Results: This boy 6 months old was diagnosed with severe acanthosis nigrican due to symptoms. When he was 6 years old, he was diagnosed with diabetes due to symptoms, laboratories work up and metformin therapy was started. His height was 106cm (<P₃) and his weight was 17kg (P₃-P₁₀). His C-peptide was over 20 ng/ml with negative autoantibodies of GADA, IAA, IA-2A and ICA. His family history was very unique. His brother was diagnosed with neonatal diabetes and died at the age of one-month. His sister with severe acanthosis nigricans died of diabetes ketoacidosis during adolescent period. A homozygous mutation (p.I348F) was found in exons 4 of the *INSR* gene.

Conclusions: This case report showed that a homozygous mutation *INSR* mutation contributed to diabetes mellitus, severe acanthosis nigricans and short stature in this Chinese child with unique family history.

P2-96**Evaluation of celiac disease antibodies and 25-OH vitamin D in type 1 diabetic patients**

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Background: In diabetic patients vitamin D seems to play a role not only on bone metabolism, but also on many other organs and/or systems, such as lipid profile, cardiovascular system, etc. We decided to evaluate whether the celiac disease antibodies in type 1 diabetic patients have a connection with 25-OH vitamin D status.

Materials and Methods: 78 young patients with type 1 diabetes were evaluated with mean age of 14±1.18, and diabetes duration of 7±0.95 years, male/female ratio was as 1/1.11. In all investigated patients HbA1c, 25-OH vitamin D, anti-tTG (tissue transglutaminase) autoantibodies were measured, as well as anamnestic data was collected. Hypo- and hyperthyroid patients were excluded. Statistical analyses were performed to determine the significance of findings. In all cases null hypothesis was rejected if p<0.05.

Results: From 78 investigated patients 45 (57.7%) showed to have vitamin D deficiency <20ng/ml. In the rest 42.7%, who had sufficient vitamin D level, it was >20-30ng/ml, which indicates that they have so called "low-sufficient" vitamin D status. No connection between vitamin D status and sex, as well as the diabetes duration was found (p>0.05). HbA1c was significantly high in vitamin D insufficient group (p<0.05). Interestingly no significant difference is found in anti-tTG titers between vitamin D sufficient and insufficient groups (p>0.05), indicating no connection between 25-OH vitamin D and anti-tTG levels. High titers of celiac antibodies also were not associated with poor glucose control (p>0.05). But HbA1c revealed to correlate with age (p<0.05).

Conclusions: Glucose control in type 1 diabetic patients correlates with age, as well as is associated with vitamin D status in the organism. No connection between celiac disease antibodies and vitamin D status was found in type 1 diabetic young patients. Further studies are required more profoundly to investigate other parameters' and complications' connection with celiac disease and vitamin D status in type 1 diabetes.

P2-97**Does commencing on an insulin pump improve glycaemic control in paediatric patients?**

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Background: Long-term outcomes in diabetic patients are associated with good glycaemic control. In the UK, the National Institute of Clinical Excellence recommends that insulin pump therapy is used for patients when multiple injections are impractical or inappropriate (Guideline 151, 2008). However, insulin pumps are very expensive and some previous studies do not suggest a significant improvement in glycaemic control compared with

multiple injections. The aim of our study was to examine if a cohort of patients had improved glycaemic control after commencing insulin pump therapy.

Methods: All paediatric patients on continuous insulin pumps at our centre were identified in November 2017. Demographic data was collected from each patient. Glycaemic control (HbA1c) was assessed at 3, 6 and 12 months prior to commencing the pump and at 3, 6, 12, 18 and 24 months after commencing the pump. Mean and median HbA1c were calculated and changes in HbA1c were analysed by gender and age when commencing the pump. Appropriate t-test was used to assess for statistically significant differences.

Results: Sixty-six patients fit our inclusion criteria, with data available for forty-seven (71%) patients. Mean HbA1c at 12 months prior to commencing insulin pump was 59 mmol/l, mean HbA1c at 3 months prior to the pump was 58 mmol/l. Mean HbA1c at 6, 12 and 18 months following starting the pump was 60 mmol/l at each time point. There were no significant differences in HbA1c from 12 months prior to pump therapy to 18 months post therapy. There were no statistical differences for gender (p value 0.14 at 12 months after commencing pump) or age at commencing pump therapy (p value 0.83 12 months after commencing pump). Patients from a more deprived area had significantly worse glycaemic control prior to commencing pump therapy, but there was no significant difference with those from less deprived areas once pump therapy had been commenced.

Discussion: Our results showed that there was no significant improvement in glycaemic control with pump therapy. Gender and age of patient had no effect. Those from a more deprived area had worse glycaemic control prior to commencing pump therapy but this was not different from patients from more affluent areas after pump therapy had commenced. This indicates that perhaps these patients from more deprived areas need input prior to pump therapy, and all patients need more input and education after commencing on the pump.

birth weight of more than 4000 g at term. Neonatal hypoglycaemia (NH) was defined as a plasma glucose < 30 mg/dL in the first day of life and < 45 mg/dL thereafter. Data on neonatal outcome was collected the hospital records as a part of a PEARL-Peristat Study, funded by QNRF- Doha-Qatar.

Results: GDM and DM women had a higher prevalence of NM. In addition, macrosomic newborns of dysglycemic mothers had a higher prevalence of NH compared to MN of normoglycemic mothers. the major risk factors for macrosomia which were compared with the normal weight infant groups (for all parameters). (table)

Table: Macrosomia and associated hypoglycemia in Normoglycemic and dysglycemic women

Babies	Mothers		
	No DM	GDM	DM
Liveborn	8926	3018	233
NICU admissions	1076	483	58
Macrosomic babies	447	205	15
Macrosomia + hypoglycemia requiring NICU admission out of liveborn	0.078%	0.26%*	1.29%*
Macrosomia + hypoglycemia requiring NICU Admission out of all macrosomia babies	7 (1.57%)	8 (3.9%)*	3 (20%) *

*p<0.05

Conclusion: Neonatal macrosomia is still more prevalent in treated women with DM and GDM. It appears that macrosomic infants of dysglycemic mothers are in greater risk of having severe hypoglycemia requiring NICU admission compared to MN of normoglycemic women.

P2-98

Prevalence of Neonatal Macrosomia (NM) and Its Relation to Hypoglycaemia (NH) in Normoglycemic Versus Dysglycemic Pregnant Women

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Introduction: Several factors contribute to the risk of neonatal macrosomia (NM) and its associated hypoglycemia (NH) in pregnant women.

Objective: To determine the prevalence of NM and its association with NH in a large cohort of normoglycemic and dysglycemic women.

Methods: Out of 12255 pregnant women screened during 2016-2017, 3027 women were identified with gestational diabetes (GDM) (WHO criteria) and 233 were diabetic (DM) before pregnancy. All dysglycemic women were managed according to related guideline/protocol with 3 or more clinical visits during the pregnancy period. Neonatal macrosomia (NM) is defined as an infant's

P2-99

A Case of Neonatal Diabetes Due to Newly Defined Mutation in the GLIS 3 Gene

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Introduction: GLIS3 is a member of the GLI-similar zinc finger protein family encoding for a nuclear protein that maps to chromosome 9p24.3-p23. Mutations in GLIS3 have been reported in association with Neonatal diabetes mellitus and hypothyroidism syndrome. We aimed to present a case of congenital diabetes mellitus congenital hypothyroidism associated with a newly identified mutation in the GLIS-3 gene.

Case Report: A seven day old female patient was referred to our outpatient clinic because of elevated TSH level in the newborn screening program. Laboratory examination revealed hyperglycemia and hypothyroidism. There was no consanguineous

marriage between the parents. In her physical examination, her general condition was moderate to good, her skin had mild icteric and turgor decreased, she had anterior fontanel 4×3 cm, posterior fontanel 0.5×0.5 cm, no pathologic reflex and no skeletal deformity. In laboratory examination, blood glucose was 702mg/dL, insulin:2uU/ml, C-peptide:0.01ng/ml, Anti-GAD:2.5IU/mL, islet cell antibody (-), Hemoglobin A1c:7.2%, TSH:28 uIU/mL, fT4 was 0.5ng/dl. There was no acidosis in blood gases. Regular insulin was initiated as an infusion of 0.05 U/kg/h. Subsequently, NPH insulin was administered subcutaneously in 3 doses. Daily insulin dose was up to 2-3 u/kg. Blood glucose was partially regulated. At the age of two, she was followed up in our outpatient clinic, and her daily insulin requirement was approximately 1-2 U/kg. Due to the inability to regulate blood sugar, an infusion pump was considered but her family did not give consent. For hypothyroidism use 50 mcg/day levothyroxine. Two different homozygous c(1783A>C); and 1835G>C mutations were identified in the GLIS3 gene in their genetic analysis.

Discussion: Infants with neonatal diabetes are usually born at term and with low birth weight. Due to its effect on growth in the intrauterine period, insulin deficiency in these cases results in IUGR. It is known that more than half of the cases are transient and the lesser part results in permanent DM. Mutations in the GLIS3 gene are very rare and are known to cause NDM. Gene product protein embryogenesis, especially pancreatic β cells, eye, liver and kidney development, as well as the heart, skeletal muscle, stomach, brain and bone development takes place. Congenital hypothyroidism, congenital glaucoma, hepatic fibrosis and polycystic kidneys are previously described concomitant anomalies. Eye examination, hearing test, skeletal radiographs and abdominal ultrasound of our patient were normal and there was no additional finding except congenital hypothyroidism.

On admission patient was in the fair condition with symptoms of dehydration.

Patient did not complain about abdominal pain.

In laboratory tests glucose level was 530mg%, ketones 4.5 mmol/l, metabolic acidosis: pH 7.198; BE -19.5, sodium 141 mmol/l and due to lipemic blood serum triglycerides were checked and result was 13,000mg /dl (N<100 mg/dl). HbA1c level of 15%. Elevated anti-GAD and anti-pancreas antibodies were present. Lipase level and C reactive protein were tested and were elevated.

During hospitalization the patient was treated with intravenous insulin and heparin infusion, resulting in normalization of blood biochemical parameters and clinical condition of the patient. Due to elevated pancreatic enzymes with high triglycerides levels intravenous treatment was conducted longer to achieve normalization of biochemical parameters.

After three months glucose levels were well controlled and triglyceride level was 73mg/dl.

A genetic test for lipoprotein lipase mutation is planned.

Conclusions: Patients with diabetic ketoacidosis may present severe hypertriglyceridemia and be in risk of acute pancreatitis. When severe hypertriglyceridemia is diagnosed patients require individual treatment.

Study Funded: ST 120

P2-101

Evaluation of the Effect of Knowledge Levels of Adolescents Diagnosed with Type 1 Diabetes Mellitus on Hba1c and Life Quality Score

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Introduction: Type 1 Diabetes Mellitus (T1DM) is a chronic disease in children and adolescents. There are studies showing that quality of life is affected in T1DM. In our study, we aimed to evaluate the effect of diabetes knowledge levels on quality of life and metabolic status.

Methods: Patients aged >10 years who were diagnosed with diabetes mellitus in our clinic and who were given diabetes education and who had regular follow-up were included in the study. At the end of the education, all subjects and their families underwent a 20-item Diabetes Assessment Test (DAT). DAT was repeated at the beginning, 3, 6, 9 and 12 months after the diagnosis. In diagnosis, the third, 6th, 9th and 12th months after the diagnosis also consisted of five options (1 never, 5 always), 24 items and 6 dimensions Quality of Life Scale (QLS) was applied to patients. The DAT scores, QLS scores, HbA1c status were analyzed by appropriate statistical methods.

Results: The study included 15 male and 30 female patients. The mean age of diagnosis was 11.3 ± 2.2 (10-15) years, and the diagnosis HbA1c value was $\% 12.8 \pm 2.3$ (10.1-16.8). The diagnosis and follow-up HbA1c, DAT and QLS scores and p values of the cases are presented in Table 1. The DAT scores were adequate in all months. Among all months, DAT and QLS scores were similar. There was no correlation between HbA1c level and DAT score and QLS score. There was no correlation between DAT score and QLS score.

P2-100

Hypertriglyceridemia as a complication of severe diabetic ketoacidosis in newly diagnosed diabetes - a case report

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Introduction: In diabetes type 1 damage of pancreatic beta cells results in insulin deficiency and it can lead to many clinical and biochemical complications, including hypertriglyceridemia. Triglycerides level over 500mg/dl significantly increases the risk of acute pancreatitis which, in combination with ketoacidosis, can worsen the prognosis of patients.

A Case Report: A 9 year old patient was admitted to the Pediatric Diabetes Department due to severe ketoacidosis in newly diagnosed diabetes. For about 2 months he had been having diabetes symptoms, polydipsia, polyuria, nocturia and bed wetting every few days for 5 month before diagnosis. He also reported weight loss 3 kg during the last 5 months. Family history regarding dyslipidemic disorders was negative.

Table 1. Hba1c, DAT and QLS scores and p values of cases

	Beginning	3. months	6. months	9. months	12. months	p
Hba1c (%)	12,8±2,3(10,1-16,8)	6,1±1,1 (5,2-8,4)	6,2±0,6 (5,3-7,9)	6,2±0,7 (5,1-7,8)	6,5±0,9 (5,1-7,8)	0,01
DAT score	169,5 ±25,3 (90-200)	157,8 ±30,9 (75-200)	161,9 ± 30,9 (90-200)	166,4 ± 24,3 (120-200)	168,1 ± 28,6 (105-200)	0,271
QLS score	91,7 ±22,4 (47-112)	101,7±17,1 (76-115)	99,2 ± 11,6 (78-120)	98,3 ± 12,5 (74-119)	98,5 ± 14,1 (71-117)	0,606

Conclusion: In our study, we found that diabetes knowledge in our adolescents patients diagnosed with T1DM remained in adequate levels for the first year after diagnosis, and the quality of life was similar in the first year and Hba1c levels were in good metabolic control. We think that the fact that the patients know from the beginning that they are included in the study may be affected the results.

A 86.6% majority did not present any problems, 11.4%(12) break away and 2%(2) contact dermatitis. No serious adverse event attributable to the use of this technology was recorded. The economic cost during the period was about 133.685,55 euros (105 patients with flash system and 18 traditional system). Assuming an mean use of 6 test strips per day, with capillary glycemia, the expense would have corresponded approximately to 44.446,05 euros.

Discussion: Although the systematic use of FGMS implies a significant increase in public spending, the high degree of satisfaction with few problems would justify its financing.

P2-102

Flash Glucose Monitoring System Versus Blood Sugar Test Strips: Cost Comparison and Satisfaction During a Year in a Northern Spain Region

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Background: The flash glucose monitoring system (FGMS) has been a great advance in quality of life for patients diagnosed with type 1 diabetes (T1D). However, it is a more expensive method.

Objectives: To describe the characteristics of the pediatric population (<18 years) diagnosed with T1D using FGMS, during one year in our community. To assess the degree of satisfaction and possible inconveniences. To evaluate the economic cost compared with test strips.

Methods: Medical records retrospective study between 01-02-2018 and 31-01-2019. Statistical analysis with SPSS v.24

Results: The number of patients under 18 years who were followed up by T1D was 127 (63 male and 64 female). Four were excluded due to the use of other CGMS, all under 5 years old. Other 18 patients (10 male and 8 female), because they preferred traditional method of monitoring by test strips: 16 for esthetic reasons, 1 because of break away and another for contact reaction to the adhesive. Therefore, the sample consisted of 105 patients using FGMS: 26 of them, from the moment of diagnosis. The mean age at the moment of study was 12.5 ± 3.9 years: <5 years 4.7%(5), 5-11 years 35.3%(37) and 12-18 years 60%(63). The time of evolution of T1D was 4.8 ± 3.6 years. The mean age at the beginning of FGMS was 11.3 ± 3.9 years. At the time of the start of financing by the public health system, 37.1%(39) already used this system through self-financing. Of the sample analyzed, only 19.1%(20) performed frequent capillary glycemia (confirmation hypo / hyperglycemia) and 24.8%(26) never did. Confirmation of hypoglycemia: 28.6%(30) frequently and 20%(21) never. Insulin records: 50.5%(53) frequently and 1%(1) never. Degree of satisfaction: high in 86.6%(91).

P2-103

Evaluation of the association of glutamic acid decarboxylase antibody and limbic encephalitis in children with type 1 diabetes mellitus

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Glutamic acid decarboxylase (GAD) is the enzyme that catalyzes the conversion of L-glutamat into GABA, one of the classical neurotransmitters with neuroinhibitory function. GAD is present in GABAergic neurons and in pancreatic beta cells. It is remarkable that Anti-GAD antibody(Anti-GADab) can have different disease manifestations, i.e., Type 1 diabetes mellitus (T1DM), Stiff-Person Syndrome, limbic encephalitis (LE), epilepsy. Cooccurrence of T1DM and LE is reported in the literature. There is no study in the literature about the presence of LE in patients with T1DM.

We aimed to investigate the presence of LE in patients with T1DM and its association with Anti-GADab levels.

Method: Anti-GADab high positive (> 100 IU / ml), Anti-GADab low positive (10-100 IU / ml) and Anti-GADab negative (\leq 10 IU / ml), 34 cases with T1DM were included in Gazi University Faculty of Medicine Pediatric Endocrinology Department. Anti-GADab levels of the patients were evaluated retrospectively. Physical examination and electroencephalography (EEG) were performed in the pediatric neurology department. Cranial Magnetic Resonance was planned for cases with positive findings in terms of neurological examination and / or LE in EEG. All EEGs were ordered with sleep deprivation.

Results: The general characteristics of the patients are given in the table. Anti-GAD levels were correlated with HbA1c averages ($p < 0.05$). The mean HbA1c of the Anti-GADab negative cases was 8.2%, the mean HbA1c of the Anti-GADab low positive cases was 9.4%, and the mean HbA1c of the Anti-GADab high positive cases was 8.7%. A total of 34 EEG records were identified. Of the total number of records, 24(70.6%) were normal and 10 (29.4%) abnormal. There was no significant relationship between Anti-GADab levels and epileptic activity. In this summary, preliminary reports of the study were shared and study has been ongoing.

Conclusion: Our study shows that especially sleep deprived EEG may be used as an indicator of LE or autoimmune epilepsy in children with T1DM. These patients are going to be followed for long term for the development of LE in the future. Our hypothesis is the GAD autoimmunity, even after many years, can spread to the CNS. As early treatment of GAD antibody-associated CNS disorders has a better prognosis, vigilance for electroencephalographic findings indicating GAD antibody-associated CNS autoimmunity is mandatory in patients with T1DM.

Parameter	Value	
Gender (M/F)	Male	14(41.2%)
	Female	20(58.8%)
Age (on diagnosis)		6.8±2.9
		10.6±3.8
Age (Study)	≤10	8(23.5%)
	>10, ≤100	11(32.4%)
Anti GAD Level	>100	15(44.1%)

P2-104

Insulin pump therapy implementation in Uzbekistan

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Background: Devices for continuous subcutaneous insulin infusion have become fundamentally new and progressive step in the treatment of diabetes.

Aims and objectives: To evaluate the effectiveness of insulin pump therapy in comparison with the regime of multiple daily injections (MDI) of insulin.

Materials and Methods: Forty children and adolescents with type 1 diabetes from 5 to 17 years (28 girls and 12 boys) were examined. All patients were divided into 2 groups. Group 1 consisted of patients who were transferred from the baseline bolus scheme of insulin therapy with human insulin to MDI with combination of a human insulin analog and a short-acting insulin. Group 2 includes patients who were transferred to pump insulin therapy and received ultrashort acting insulins. Glycemia and glycated hemoglobin were monitored Within 12 months,

Results: The comparative analysis showed a significant decrease in glycated hemoglobin (7.9 ± 0.3) by 2.3% in group 2, compared with children and adolescents on the MDI regime (HbA1c $7.8 \pm 0.3\%$, decrease by 1.5%). The proportion of patients with

a HbA1c level of less than 7.5% on MDI increased from 20% to 50%, and in the group receiving insulin pump therapy increased from 15% to 50%. Target values of HbA1c < 7.5% reached 50% of patients in groups 1 and 2.

Conclusion: On insulin pump therapy HbA1c decreased by 2.3%. The target values of HbA1c reached 50% of the patients in both groups.

Fat, Metabolism and Obesity

P2-105

Cardiopulmonary exercise testing, body composition and metabolic status in young adults after allogeneic human stem cell transplantation for hematological malignancy in childhood

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Introduction. Well-known long-term complications of alloHSCT in childhood include endocrine system damage and secondary malignancies. In addition, adults surviving childhood alloHSCT are at risk of cardiovascular (CV) and metabolic disturbances. Long-term data of physical fitness in correlation with metabolic status are scarce in this particular group.

Objective/Patients and Methods. Cross-sectional investigation of exercise performance by cardiopulmonary exercise testing (CPET) and metabolic parameters in boys and girls (age 16–25 years), who underwent alloHSCT for a hematological malignancy in childhood, in comparison to healthy peers. Maximal oxygen consumption (VO₂peak), maximal load (PPeak), exercise duration (time), ventilatory anaerobic threshold (VAT), leptin/adiponectin ratio (L/A ratio), HOMA-IR, whole body fat and lean mass were determined. After testing for normality, data were compared using parametric (unpaired t-Test) or non-parametric (Mann-Whitney U-Test) tests. Pearson correlation test was used to evaluate correlations between metabolic and physical fitness parameters.

Results: Twenty-one patients (11 males, 10 females, age 20.3 ± 3.3 yrs, weight 58.4 ± 9.6 kg, length 166.9 ± 6.8 cm, BMI 21.0 ± 3.3) and 21 controls (11 males, age 19.4 ± 3.0 yrs, weight 61.8 ± 9.0 kg, length 169.0 ± 6.1 cm, BMI 21.5 ± 2.7) participated. In the patient group, mean age at time of alloHSCT was 9.2 ± 4.9 years. Indications for alloHSCT were ALL (n=15), AML (n=2), CML (2), ALCL (n=1) and MDS (n=1). Maximal heart rate was not different in both groups (183.6 ± 9.8 bpm vs. 187.8 ± 19.6 bpm, NS). AlloHSCT patients had lower maximal oxygen consumption (VO₂peak, 32.7 ± 9 ml/kg/min vs. 38.8 ± 6 kg/min, $p < 0.05$), shorter exercise duration (9.0 ± 2.5 min vs. 13.1 ± 2.8 min, $p < 0.001$), lower maximal load (%PPeak 82.5 ± 47.3 vs. $112.6 \pm 34.6\%$, $p < 0.001$) and different aerobic threshold ($66.9 \pm 17.4\%$ vs. $50.2 \pm 9.2\%$, $p = 0.001$). HSCT-patients had higher L/A ratio (4.24 ± 5.91 vs. 1.55 ± 1.22 , $p < 0.05$), HOMA-IR (2.63 ± 1.69 vs. 1.78 ± 0.46 , $p < 0.05$), whole body fat mass (16.360 ± 7.2 kg vs. 14.206 ± 5.496 kg, $p < 0.01$) and lower whole body lean mass

($41.270 \pm 9.430 \text{ kg}$ vs. $46.664 \pm 6.430 \text{ kg}$, $p < 0.05$). L/A ratio, whole body fat mass and whole body fat percentage were negatively correlated with VO₂peak ($\rho = -0.57$, $p < 0.01$; $\rho = -0.66$, $p = 0.001$ and $\rho = -0.71$, $p = 0.001$, respectively). No correlation between HOMA-IR and VO₂peak was withheld.

Conclusions: Young adults after HSCT have lower maximal exercise performance and a less favorable metabolic profile in comparison with healthy children. Leptin/adiponectin ratio, whole body fat mass and whole body fat percentage are negatively correlated with physical fitness, stressing the importance of healthy lifestyle promotion and physical rehabilitation in this patient population.

P2-106

School-age children awareness of seriousness of obesity problem, health-related outcomes and effectiveness of self-control preventive strategies

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Background: Childhood obesity is a serious medical condition that may well be prevented by the life style modification. Therefore school-age children awareness of the problem is crucial for the educational programs.

Subjects Methods: This work is a part of the complex project "Assessment of the current nutritional status, nutrition-related health problems in school-age children in Ukraine". 392 school-age children were included and grouped by the age: primary school (aged 6–9, n=75), secondary school (aged 10–14, n=202) and high school (aged 15–18, n=115). Original questionnaire was elaborated for the survey and consist of both multiple choice questions and «open questions» that encouraged children to give their own idea with the purpose of understanding a real awareness of the problem. Answers to the open questions about the causes and effects of obesity were analyzed. Standard statistics used to assess the results.

Results: Awareness of seriousness obesity problem gradually increases with age (primary school – 58,67%, secondary school – 70,51%, high school – 91,67%, $p < 0,05$). One third of respondents regardless of age (primary school – 29,31%, secondary school – 29,21%, high school – 33,04%, $p > 0,05$) understand that obesity can cause serious health-related problems and the most detrimental changes occur in the cardiovascular system.

We discovered that secondary-school children are less worrying of having obesity whereas more than half of high-school children are positive concerning obesity likelihood in them ($p < 0,05$).

Self-controlled situations is a main causative of the obesity for more than half surveyed children (53,33% of primary school, 53,46% of secondary school children and 41,74% high school children, $p > 0,05$). Portion size as effective method of the obesity prevention was mentioned by 38,67% of primary school, 48,08% of secondary school children and 75,0% high school children, ($p < 0,01$). Meantime just 30-40% of respondents have an experience of the portion size control and 15-20% do it episodically ($p > 0,05$). Lack of experience and circumstances such as busy time-table were named as a main barrier for that.

Less than 10% of children are not aware of the causes of obesity and possible outcomes. Meantime, 30% of respondents were not compliant with the survey.

Conclusions: Regardless of age school-children are aware of seriousness of obesity problem, health-related outcomes and effectiveness of self-control preventive strategies. Special education is necessary with the purpose of gaining relevant life style skills.

P2-107

Childhood Obesity and Iron Metabolism

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Introduction: Hypoferraemia is the most common nutritional deficiency worldwide and a leading cause of potential developmental disorders in children. Obesity seems to be associated with this condition, but it is still unclear if it is caused either by depleted iron stores, diminished availability, or both.

Aim: To analyse the relationships between childhood obesity, iron metabolism and inflammation.

Methods: A six-month cross-sectional study was conducted on a convenience sample of otherwise healthy, obese children and adolescents referred to two tertiary level paediatric obesity clinics. Evaluated variables: body mass index (BMI), iron intake (7-day diet records before blood sample), serum iron, transferrin receptor, ferritin and high sensitivity C-reactive protein. Data were analysed using covariance and multiple linear regression models with a significance level: $p < 0.05$.

Results: Of 272 patients (51% female, 92% Caucasian) 37% were overweight and 21% were obese. Characteristics linked to the overweight and obese group ($p < 0.05$) were: higher heme iron consumption, lower non-heme iron and vitamin C ingestion; lower serum iron, iron deficiency (higher transferrin receptor) and inflammation-induced iron sequestration (higher ferritin and C-reactive protein). There were no differences in total daily iron intake or other dietary factors important to its absorption between groups. High transferrin receptor and iron sequestration contributed independently as predictors of low serum iron. On the other hand, neither total dietary iron intake nor BMI was an independent predictor factor.

Discussion: As previously demonstrated in adult studies, in children the hypoferremia of obesity occurs both by true iron deficiency and by inflammatory-mediated functional iron deficiency.

Keywords: Iron, Inflammation, Obesity, Paediatrics

P2-108**Effectiveness of Multidisciplinary Outpatient Approach in the Management of Paediatric Obesity**

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Background: A meta-analysis of 39 studies using multicomponent lifestyle interventions, in comparison to standard, minimal, or no treatment identified a mean difference in BMI z-score of -0.12 (95% CI -0.17 to -0.06) at six months. However, a minimum BMI-SDS reduction of 0.25 or greater has been shown to improve metabolic health in overweight children. We describe our experience in a multidisciplinary (MDT) clinic at a tertiary children's hospital with tier 3 level of care for obesity.

Methods: We retrospectively reviewed records of new patients seen on two or more occasions in our obesity clinic from October 2017 to September 2018. Our tier 3 set-up was radically changed two years ago to incorporate a specialist nurse, paediatric psychologist and social worker in addition to medical staff and paediatric dietitians. The first visit includes a detailed medical, dietary, behavioral and physical activity history, physical examination and blood tests. Henceforth, the emphasis is on family education with respect to diet, physical activity and lifestyle choices. Biopsychosocial factors are assessed and addressed directly by the extended team. Simple, achievable and sustainable lifestyle changes and targets are suggested at each visit (2-monthly) which are gradually revised as necessary until they became a part of daily lifestyle. No one member of the team leads, all contribute equally, but with each family one or two members may become predominant in leading change.

Results: 26 (16 males) out of 44 children were seen at least twice and were included in the analysis. The presentation age ranged from 4 to 16 years (mean 10.6). The first visit BMI SDS ranged from 2.03 to 5.28 (mean 3.41). Their follow up period ranged from 2 months to 9 months (mean 6 months). The mean BMI SDS during this follow-up period was 3.14, showing a 0.27 reduction (95% CI -0.478 to -0.064). Follow up BMI SDS dropped in 20 children (77%), remained the same in one (4%) and increased in five children (19%).

Discussion: Extra personnel enabling a whole-systems approach to weight management with realistic goal setting achieved a mean BMI SDS improvement of -0.27 at six months, improving on a recent meta-analysis of trials (-0.12). However, even with the best support, it may be a challenge to achieve or sustain BMI reductions due to lack of motivation, frustration and social issues. Continuing efforts and further innovative strategies need to be identified to improve and maintain the outcomes.

P2-109**Metabolic syndrome in children and adolescents who survived after childhood cancer**

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Background / Objectives: During treatment of children and adolescents with cancer, an imbalance of carbohydrate and mineral metabolism may occur, leading to clinical manifestations of the components of the metabolic syndrome. The aim of the work was to study the frequency and severity of various clinical signs associated with metabolic syndrome in a cohort of patients from the Russian Field Clinical Rehabilitation Center.

Design / Methods: A group of 100 surviving leukemia patients and 160 children of the survivors of the posterior cranial fossa in 2017–2018 were formed through an exhaustive clinical examination, including toxicity analysis of chemotherapy, family history, and physical and psychological status. In general, more than 50 characteristics were determined in all patients, including biochemical parameters, such as insulin level, HOMA index, lipid profile, etc., as well as BMI, bio-impedance, exercise tolerance, sphygmometry, psychological testing. Statistical analysis was performed using the software package Statistica 8.0 (StatSoft Inc., USA).

A decrease in high-density lipoprotein levels was observed in 65% of patients; increased BMI in 44% of patients, which corresponded to the disproportion of adipose and muscle tissue. Insulin resistance, defined as a HOMA index higher than 3.2, was registered in 21% of patients, and arterial hypertension in 16% of patients. There are trends that obesity, insulin resistance and arterial hypertension adversely affect physical and psychological status. Genetic testing of surviving leukemia patients revealed a statistically significant association of rs11091046 polymorphisms in the AGTR2 and rs4833095 gene in the TLR1 gene with insulin resistance developed after chemotherapy.

Thus, the described algorithm allows identification of a combination of three potential components of the metabolic syndrome in 30% of survivors of childhood cancer. The findings can contribute to the development of an individual rehabilitation program for the prevention and treatment of metabolic syndrome in patients receiving anti-tumor therapy in children.

P2-110**Pubertal milestones and related hormonal changes among children with obesity**

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Background and Objective: Obesity is known to affect pubertal timing. However, existing data are still controversial, observing either delayed or accelerated pubertal onset, especially among boys. Herein, we evaluated pubertal milestones and underlying hormonal changes between lean and obese children.

Material and Methods: We examined 13,484 events from 4,855 lean (BMI SDS < 1.28) and 1,983 obese (BMI SDS > 1.88) children aged 5 to 20 years. The onset of pubertal milestones (breast stage (B) ≥ 2, pubic hair stage (PH) ≥ 2, testicular volume ≥ 4ml, age of menarche) was analyzed by both survival analysis (encompassing interval-censored, right- and left-censored data), as well as direct comparison of prepubertal vs. pubertal events within a one-year-resolution. Observations were compared with dynamics of puberty-related hormone levels.

Results: Among girls with obesity, the estimated median onset of thelarche was 9.86 years, compared with 10.18 years in lean girls. Furthermore, 13.9% of obese girls exhibited already breast development (B ≥ 2) at the age of 7 years, compared with only 1.2% of lean girls. In addition, obesity reduced the average age of menarche about 6 months (12.22 (± 1.30) vs. 12.76 (± 1.18) years). Surprisingly, those differences were not paralleled by altered estrogen or gonadotropin levels. However, earlier development of pubic hair among obese vs. lean girls (15.3% vs. 0% had PH ≥ 2 at the age of 7 years) was associated with higher testosterone and DHEA-S levels within the same age group.

Regarding boys, no clear association between BMI and the onset of testicular growth could be observed. On the other hand, development of pubic hair started earlier comparing obese boys with lean peers (6.4% vs 2.7% with PH ≥ 2 at 8 years of age) and was associated with increased DHEA-S levels but no difference in testosterone levels.

Conclusion: Pubertal milestones were accelerated among girls with obesity when compared with lean peers. No clear association of BMI and pubertal onset (gonadarche) could be detected for boys. Pubarche occurred earlier among both obese girls and boys and was associated with higher DHEA-S levels. Those findings should be kept in mind, when distinguishing between physiological and pathological patterns of pubertal development among children with obesity.

P2-111**Osteoprotegerin and metabolic status in children with obesity**

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Objective: determination of changes in metabolic status and osteoprotegerin concentrations in obese children.

Methods: We examined 120 children in the University Hospital (Minsk) from 2017 to 2019 yrs. Their anthropometric parameters (height, weight, body mass index (BMI)) were determined. Blood levels of osteoprotegerin (OPG), insulin were determined. In the biochemical blood test, the parameters of uric acid, insulin were evaluated.

All children were divided into 2 groups: group 1 children with morbid obesity - 40 patients (23 boys(B)/ 17 girls(G)) (BMI more than 99th percentile for sex and age) (BMI 33.04 ± 4.67 kg/m², age 13.17 ± 2.42 years); group 2 - 30 patients (B/G=34/38) with alimentary obesity (BMI-95-99th percentile for sex and age) (BMI 27.60 ± 2.06 kg/m², age 13.43 ± 2.27 years). The control group consisted of 50 patients (B/G=24/26) with normal body weight (BMI 19.86 ± 2.24 kg/m², age 13.32 ± 2.30 years).

Results: In the subgroups of boys with obesity, there were significant differences in the concentration of uric acid in comparison with the control (alimentary obesity 426.55 ± 62.25 mmol/l vs 242.58 ± 49.90 mmol/l ($p=0.01$)), morbid obesity 324.10 ± 59.33 mmol/l vs 242.58 ± 49.90 mmol/l ($p=0.01$)). Girls with obesity have a significant increase in uric acid level in comparison with the control group (alimentary obesity 328.10 ± 51.43 mmol/l vs 213.0 ± 39.64 mmol/l ($p=0.0001$), morbid obesity 409.04 ± 84.23 mmol/l vs 213.0 ± 39.64 mmol/l ($p=0.0001$)).

In boys with obesity higher concentrations of OPG were detected relative to the control group (alimentary obesity 21.89 ± 2.17 ng/ml vs 18.1 ± 1.21 ng/ml ($p=0.05$), morbid 22.22 ± 2.14 ng/ml vs 18.1 ± 1.21 ng/ml ($p=0.03$)).

In boys with obesity higher concentrations of insulin were detected relative to the control group (alimentary obesity 18.9 ± 12.7 μ U/ml vs 9.1 ± 4.2 μ U/ml ($p=0.0001$), morbid 28.71 ± 7.36 μ U/ml vs 9.1 ± 4.2 μ U/ml ($p=0.001$)). In girls with obesity, the concentration of insulin relative to the control group was (alimentary obesity 20.28 ± 6.25 μ U/ml vs 14.10 ± 6.80 μ U/ml ($p=0.001$)) morbid obesity 23.32 ± 9.65 μ E/ml vs 14.10 ± 6.80 μ U/ml ($p=0.001$)).

Conclusion: Children with obesity have an increase in insulin and OPG rates.

P2-112**Identification of a novel heterozygous missense mutation in low-density lipoprotein receptor gene (*LDLR*) p.(Met652Thr) in an Emirati family with familial hypercholesterolaemia (FH), observed genotype-phenotype correlations and pharmacotherapeutic approaches***Lara Al-Olabi, Sara Suliman, Hinda Daggag*

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Background: Familial Hypercholesterolaemia (FH) is a common autosomal dominant disorder of low-density lipoprotein (LDL) metabolism characterised by elevated levels of plasma LDL-cholesterol (LDL-C), accelerated atherosclerosis and premature cardiovascular disease (CVD). In the Gulf Co-operation Council states, CVD is often diagnosed at a younger age and is the leading cause of mortality. As such, early genetic diagnosis and treatment of FH is important for risk stratification and aggressive targeted treatment to lower LDL-C in affected individuals, to reduce the risk of arterial disease and premature CVD outcomes.

Aims: 1. To identify FH-causing genetic variant(s) in this family including an individual diagnosed in adolescence and an individual with premature CVD. Successful genetic diagnosis will allow subsequent cascade screening in relatives.

2. To treat genetically proven FH-positive individuals with lipid lowering therapy at an earlier age.

Methods: Detailed family history was recorded and clinical and biochemical data were collected. Genomic DNA from a 54 year old female with hypercholesterolaemia (pre-treatment LDL-C=6.4mmol/L) was tested for variants in the known FH genes by next generation sequencing, followed by targeted mutational analysis by Sanger sequencing in affected family members.

Results: DNA sequencing of *LDLR* in the proband detected compound heterozygous mutations: a non-deleterious p.(Thr62Met) variant and a likely pathogenic p.(Met652Thr) missense variant; the latter was demonstrated to be maternally inherited.

Familial segregation analysis was performed; results demonstrated that the p.(Met652Thr) mutation is inherited and segregates with the disease phenotype and lipid profiles in the mother, sister and a 24 year old nephew of the proband. Prediction of the damaging effect at the protein level of the mutation p.(Met652Thr) was assessed using 3 *in silico* tools and predicted to be deleterious, not tolerated and probably damaging and thus is most likely pathogenic. LDL-C levels dropped significantly to near normal levels in response to Statin/Ezetimibe combination therapy in both proband and her mother.

Conclusions: We describe an Emirati family with clinical and biochemical features characteristic of FH, carrying a novel heterozygous *LDLR* mutation. This study highlights the importance of genetic diagnosis especially in a pre-symptomatic early age as demonstrated here in the nephew who was asymptomatic and not treated prior to genetic testing. The knowledge of the underlying genetic mutation will aid in effective treatment, family member testing, genetic counseling, and a better understanding of the effect of *LDLR* mutations on the response to pharmacological treatment to reduce the risk of morbidity and mortality.

P2-113**Prevalence and correlation of Non alcoholic fatty liver disease (NAFLD) with serum Alanine Aminotransferase (ALT) levels in obese Indian children***Archana Arya, Hriday De, Vasundhara Chugh*

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Aims: Non-alcoholic fatty liver disease (NAFLD) is the asymptomatic involvement of liver due to fatty infiltration of hepatocytes seen commonly in obese children. Elevated serum aminotransferase level serves as a surrogate marker of NAFLD. The recommended ALT cut-offs for screening for NAFLD in obese boys and girls are 22 and 25U/L respectively. We determined the prevalence of NAFLD amongst obese children in our population based on Liver Ultrasonography(USG), and determined the correlation of NAFLD with ALT levels and dyslipidemia in these children.

Methods: In this retrospective study, data from 223 obese children aged 1-18 years, with no other liver or chronic disease was analyzed. Body mass index, ALT, Fasting lipid profile, blood glucose and HbA1C were measured in all the subjects. NAFLD was diagnosed by ultrasonography. Presence of dyslipidemia was identified by any abnormality in the lipid profile as given below.

	Abnormal, mg/dl
Total cholesterol	≥200
LDL Cholesterol	≥130
Triglycerides	≥100
<10y	≥130
10-19y	<40
HDL Cholesterol	

Abnormal values represent the 95th percentile, HDL cholesterol represents the 10th percentile.

Result: We found a very high prevalence of NAFLD (40.8%) in our obese population based on USG. 71.4% children with NAFLD had associated dyslipidemia. We also found a very high prevalence of NAFLD in the group with ALT<22 in girls (33%) and ALT<25 in boys (25%).

Percentage of children with NAFLD in relation to ALT levels and it's correlation with dyslipidemia.

Girls

ALT (U/L)	≤22	>22-40	> 40	Overall
NAFLD (USG)	33.33% (15/45)	34.14% (14/41)	55.5% (20/36)	40.16% (49/122)
Dyslipidemia	73.33% (11/15)	42.85% (6/14)	85% (17/20)	69.3% (34/49)

Boys

ALT U/L	≤25	>25-40	>40	Overall
NAFLD (USG)	25% (10/40)	22.2% (6/27)	76.47% (26/34)	41.5% (42/101)
Dyslipidemia	70%(7/10)	33.3% (2/6)	84.61% (22/26)	73.8% (31/42)

Conclusion: The prevalence of NAFLD in obese children based on Liver USG in our population was very high (40.8%). Although USG may not be a very reliable way of diagnosing NAFLD, it is a warning to monitor for progression of liver disease in these children. We also found that 25/85 (29.4%) girls and boys with ALT levels below the recommended cut-offs of <22 and 25U/L respectively had NAFLD. This is a fairly large number of children in whom liver disease may be missed out if we follow the recommended ALT cut-offs. Hence we recommend that in our population all obese children should be screened for NAFLD by USG irrespective of the ALT levels.

P2-114

Five Years' Follow-up of the Effect of Sex Steroid Hormone on Lipid and Glucose Metabolism in Girls with Turner Syndrome

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Objective: We sought to evaluate the role of long-term HRT on the lipid profile and glucose metabolism in girls with TS.

Design: A pre-test/post-test observational study.

Setting: Pediatric TS clinic in The First Affiliated Hospital, Sun Yat-sen University.

Patients: 56 girls with TS had accurate maintenance HRT data.

Main Outcome Measures: Parameters of health surveillance derived from clinical guidelines.

Results: Lipid parameters did not differ during the 5 years of follow-up based on HRT or artificial cycles. Fasting glucose significantly decreased starting in the first year of HRT ($P_{1^{\text{st}} \text{ yr}} = 0.026$; $P_{2^{\text{nd}} \text{ yr}} = 0.018$; $P_{3^{\text{rd}} \text{ yr}} = 0.005$; $P_{5^{\text{th}} \text{ yr}} = 0.041$), and the fasting insulin level and homeostasis model assessment of insulin resistance (HOMA-IR) were significantly lower starting in the second year than those values before HRT (serum insulin: $P_{2^{\text{nd}} \text{ yr}} = 0.046$; $P_{3^{\text{rd}} \text{ yr}} = 0.032$; $P_{5^{\text{th}} \text{ yr}} = 0.008$; and HOMA-IR: $P_{2^{\text{nd}} \text{ yr}} = 0.037$; $P_{3^{\text{rd}} \text{ yr}} = 0.014$; $P_{5^{\text{th}} \text{ yr}} = 0.006$, respectively).

Conclusion: Sex steroid HRT was beneficial for glucose metabolism in long-term follow-up, particularly after 1 year of treatment. HRT did not affect lipid metabolism in girls with TS. Use of artificial cycles did not affect the glucose or lipid profile.

P2-115

The prevalence of severe obesity and related comorbidities has increased during the last decade among children and adolescents referred for evaluation at the obesity clinic

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Background/Aims: Childhood obesity has increased markedly during the past decades.

The aim of the study was to examine the changes in trends of severe obesity and related comorbidities among children and adolescents referred for evaluation at the obesity clinic in a tertiary care center in Israel.

Methods: The study included patients aged 2-18 years referred for evaluation due to obesity (BMI > 95th percentile) between 2008-2017. Their medical files at their first visit at the obesity clinic were reviewed for demographic, anthropometric, and cardiometabolic data. The study cohort was divided into two subgroups: those with severe obesity (BMI-SDS ≥ 2.33) and those with $2.33 > \text{BMI-SDS} \geq 1.645$. The anthropometric and obesity related comorbidities were compared between these two subgroups, and the yearly rate of severe obesity was evaluated.

Results: Of the 1027 children (median age 10.8 years, 41.8% males) fulfilling study inclusion criteria, 565 (55%) were classified with severe obese. The rate of severe obesity has increased during the years 2010-2017, although it seems that rates are plateauing during the last 2 years.

On comparison between the subgroups: in those with severe obesity there was a significant male predominance (60.6% vs. 51%, $p=0.002$) with a significantly younger age of onset of obesity, and significantly higher prevalence of family history of obesity, although statistically significant only in males ($p<0.001$ and $p=0.01$, respectively). The rates of obesity related comorbidities (systolic hypertension, obstructive sleep apnea and non-alcoholic fatty liver disease) were significantly higher in the subgroup with severe obesity ($p<0.001$).

Conclusions: Our data demonstrate that the rate of severe obesity among the Israeli pediatric population referred for evaluation at the obesity clinic is in rise, that may reflect the rising rate of pediatric severe obesity in Israel, or a change in the policy of referral by the general pediatrician. Also, the rate of obesity related comorbidities in our cohort was significantly higher in those with severe obesity. These findings should emphasize the importance of prevention of severe obesity to prevent devastating obesity related comorbidities in children and adolescents.

P2-116**Nonalcoholic Fatty Liver Disease in Pediatric Obese Patients**

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Background: Nonalcoholic fatty liver disease (NAFLD) represents one of the most important chronic liver diseases and it is an important component of the metabolic syndrome in obese patients. As severity, it includes several clinicopathological entities such as simple steatosis, nonalcoholic fatty liver (NAFL), nonalcoholic steatohepatitis (NASH) and NASH cirrhosis.

Aims of study: To evaluate the presence of NAFLD diagnosed in obese children (BMI >97th percentiles for age and sex) and the metabolic complications associated to it.

Material and Method: The study took place in the Endocrinology Department of Children Hospital, Timișoara, România between June 2017 and December 2018. Obese patients (age 3-18 years old) diagnosed with NAFLD based on the ESPGHAN guidelines (ultrasound aspects characteristic to steatosis or steatohepatitis, without any history of alcohol consumption and no liver diseases associated) were studied. They were anamnestic (gestational age, birth weight, birth height), clinical (liver size, acanthosis nigricans, blood pressure), anthropometrical (weight, height, BMI, abdominal circumference), biological (liver enzymes, lipidic and carbohydrate metabolism, OGTT test, HOMA-IR) and imagistic (liver ultrasound and Fibroscan) evaluated.

Results: Out of 126 obese patients admitted in this department during the study period, 27 children (mean age=16.3±2.9 years) were diagnosed with NAFLD (21.42%). Most of these patients (74.07%) were adolescent, half of them were boys and a quarter small for gestational age. Out of the studied patients, 55.55% had NAFL, 14.81% NASH and the rest was diagnosed with steatosis. At FibroScan evaluation, 51.85% of children were identified with minimal fibrosis and in 18.51% of them moderate fibrosis was found. The median of liver stiffness value was 7.6 (5.5–9.3) kPa. Regarding the carbohydrate metabolism, most of them had insulin resistance (74.07%), altered OGTT was identified in 66.67% of cases and increased C peptides value in 44.44% of patients. They all have at least one of the components of the metabolic syndrome: increased triglycerides value (81.48%), decreased HDL cholesterol (70.37%), hypertension (88.88%), impaired glucose tolerance (66.67%), with a mean waist circumference measured of 94.7 cm. 70.37% of patients were diagnosed with the metabolic syndrome. Diet was recommended to all children, Metformin was prescribed in 74.07% of cases, while antihypertensive drugs in 88.88% of patients

Conclusions:

1. Pediatric obesity is increasingly lately.
2. Due to its tendency to progress, early diagnosis and treatment of NAFLD are important issues at all ages.
3. Fibroscan is a non-invasive tool with satisfactory accuracy to estimate NAFLD in obese children.
4. Treatment should address not only the NAFLD itself but also the entire spectrum of comorbidities of obesity.

P2-117**Trends in childhood obesity, underweight and short stature among urban school children in Romania**

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Background: Childhood adolescence overweight and obesity are increasing in Romania, but limited information is available on their current trends.

Aim: the current study aimed to analyze the trend in prevalence of weight disturbances and stunting in the past 5 years in school aged children from the Transylvania region in Romania.

Material and Methods: Two cross-sectional data sets from 2013 (1129 subjects) and 2018 (3173 subjects) were analyzed, both including children from 6 to 14 years, from urban schools in Mureș county, Romania. Data on age, gender, height, weight and body mass index (BMI) was collected. All anthropometric measurements were carried out by trained personnel using standardized instruments. Standard deviation scores for height and BMI were calculated using the national synthetic standards for height and the WHO standards for BMI. Overweight was defined as BMI >1SD, obesity as BMI >2SD, underweight as BMI below -2SD and short stature as height below -2SD for age and sex. The prevalence of weight and height disturbances was calculated for both data sets, according to gender and age group. For data analysis M.O Excel and SPSS v. 25 were used with a level of significance $\alpha=0.05$.

Results: Gender and age distribution were similar in the two data sets ($p=0.071$ for gender, and $p=1.000$ for age). Prevalence of overweight increased in all age groups and both sexes, from 18.95% in 2013 to 22.63% in 2018, with the highest value for the pubertal age group (12-14 years). Obesity prevalence increased overall from 11.96% to 12.1%, but this was caused by an increase only for male gender, as the prevalence of obesity in girls decreased from 9.39% in 2013 to 8.84% in 2018. Prevalence of stunting decreased in both sexes from 3.99% to 1.51%. Underweight had a positive trend, with a prevalence of 1.42% in 2013 and 3.97% in 2018, with gender having no influence ($p=0.424$).

Conclusion: Both overweight and underweight have a positive trend, while stunting is decreasing in frequency. Obesity has a positive trend in boys, but is decreasing in girls, albeit the difference being rather small.

Keywords: obesity, underweight, prevalence, trend, Romania, urban

P2-118**Impact of a comprehensive program, on prevalence of childhood obesity in Andalusia, Spain**

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Introduction: Childhood obesity means a Public Health problem. It is related to chronic diseases in adults, a decrease in quality of life, and an increase in social and sanitary costs. In Spain, the National Health Service (ENSE 2017) stood the prevalence of overweight in toddler between 2 to 7 years old, in 18,26% and obesity in 10,30%, no differences between sex. In 2015 the prevalence of overweight and obesity in childhood are 21, 3 % and 6, 2 %, respectively. In Andalusia, PIOBIN: Integral Program against Childhood obesity in its lines of action, promotion of breastfeeding, healthy diet, exercise and interventions in families, are dedicated to reduce the prevalence of this epidemic.

Purpose: Analyzing the variation of prevalence of overweight in Andalusia, based on criteria of International Labour Organization, finding the relationship between the preventive activities and PIOBIN.

Methods: Descriptive cross-sectional study, in the Andalusian population in 2014 to 2016.

Results: From 2014 to 2016, the activities in promotion of healthy ways of life have been increased (The Fruit Plan at schools, involved 271291 to 396029 students, and Community Activities, increased from 205 to 320, respectively). On the other side, individual and group activities decreased in 18, 5% and 16%. Overweight and obesity, decreased from 24, 6% to 21,3%, and from 8,9% to 6,2% (OIT criteria)

Conclusions: Multidisciplinary structured interventions may help in the decrease of the prevalence rate in overweight in Andalusia.

P2-119**Evaluation of Fetuin-A level and related factors in obese adolescents**

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Objective: Fetuin-A has many different functions due to its ability to bind to different toll-like receptors in different tissues. Working in different groups will contribute to our understanding of the pathophysiology of Fetuin-A. In this study, we aimed

to evaluate Fetuin-A levels in obese adolescents and the relationship between Fetuin-A and anthropometric data, insulin levels and high sensitivity CRP(HSCRP).

Material and Method: The study included obese adolescents with BMI-SDS>=2 and healthy adolescents with similar age and gender. Anthropometric measurements, fasting glucose and insulin, HSCRP and Fetuin-A levels were evaluated.

Results: The data of the cases and comparison with healthy subjects are presented in Table 1. In obese cases, SGOT-SGPT elevation in two subjects, hypertension in 15 and hepatosteatosis in 33 patients were found to be present. Glucose intolerance was detected in four cases and diabetes mellitus in one patient. Insulin, HOMA-IR and HSCRP levels of obese subjects were significantly higher and Fetuin-A levels were similar. There was no significant difference between hyper and normotensive subjects ($p = 0.643$). There was no significant difference between subjects with or without fatty liver ($p = 0.967$). Patients with and without insulin resistance according to HOMA-IR fetuin-A levels were similar ($p = 0.231$). When we evaluated the correlation between Fetuin-A levels and OGTT results in 0-30-60-90-120 minutes, we found that there was no significant relation. No significant correlation was found between fetuin-A and HSCRP in the groups.

Conclusion: Although the Fetuin-A levels were found to be high in obese subjects in children and adult studies; in this study, no difference was found in serum Fetuin-A levels in obese and healthy subjects in adolescent age group. This result was thought to be related to homogenization of selected cases to adolescents with physiological differences. We believe that our study will shed light on further studies.

Table 1. Data of cases and comparison with healthy subjects

	Obese(n:41)	Healthy(n:30)	p
Gender	27 female,14 male	22 female,7 male	
Age(year)	15,3±2,1 10,5-18	14,3±2,1 10,3-17,8	0,063
Height sds	0,33±1,4 -1,9-(+4,3)	-0,14±0,7 -1,6-(1,1)	0,073
BMI(kg/m2)	33,1±4,2 26,4-42,9	21,5± 2,2 17-25	0,000
BMI sds	2,8±0,55 2-4,5	0,4±0,7 -1,3-(+1,4)	0,000
Fasting glucose (mg/dl)	94,7± 8,8 76-115	91,2±7,9 71-106	0,087
Fasting insulin (μIU/ml)	27,2±15,4 8,7-81,5	13,4±7,2 4,6-30,8	0,000
HOMA-IR	6,3±3,7 1,7-17,5	3,1±1,8 1,0-7,2	0,000
Fetuin-A (ng/ml)	453±200,2 206,6-1112,12	484,2±160,7 114,1-923,9	0,481
HSCRP (mg/dl)	0,3±0,2 0,-0,5	0,16±0,16 0,-0,5	0,012

P2-120**Prevalence of Obesity among Infants Presenting with Intussusception**

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Background: Intussusception is a life-threatening illness, with incompletely understood etiology, although some predisposing factors are known. Intussusception frequently occurs in well-nourished chubby infants.

Aims: We aimed to determine whether patients presenting with intussusception have a high prevalence of obesity.

Patients and Methods: This cross-sectional study was conducted in 100 infants presenting with intussusception aged ≤ 2 years at the Pediatric Surgery Department. Anthropometric measures, history of recent upper respiratory tract infection, timing and type of intervention were recorded. Obesity was defined as having a body weight for length ≥ 97.7th centile on WHO growth charts.

Results: The study comprised 58 boys and 42 girls, 31% of whom had an upper respiratory infection in the preceding month. Obesity was present in 18% of patients, based on WHO growth charts. There was a trend towards a higher percentage of obese infants within the younger (25%) (aged <8 months) compared to older age groups (12%, $P = 0.085$), but with no gender difference. Obesity did not influence the success rate of hydrostatic reduction. The percentage of infants with a weight-for-age centile ≥85th was 42%, of whom 7% were ≥97.7th centile based on Egypt-specific growth charts. The corresponding percentages for the weight-for-length were 29% and 15% of patients respectively.

Conclusion: There is a high prevalence of obesity in infants presenting with intussusception, more so under 8 months of age. The mechanistic link between obesity and the pathogenesis of intussusception deserves investigation.

P2-121**A non-invasive model for detection of the metabolic syndrome in children and adolescents**

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Objectives: We aimed to develop a non-invasive model for the detection of metabolic syndrome (MetS) in school children and adolescents.

Methods: Participants were 7,330 children and adolescents aged 10–18 years attending schools in eight Chinese cities. Participants had anthropometry measured by research nurses and underwent fasting blood tests. MetS was defined as central obesity (waist-to-height ratio ≥0.46 for boys and ≥0.48 for girls), and a combination of abnormal glycaemia, hypertension, and/or dyslipidaemia. A prediction model for MetS was developed using multivariable logistic regression using non-invasive anthropometric and clinical parameters.

Results: Overall, MetS prevalence was 3.9%. The prediction model included age, waist-to-height ratio, hypertension, acanthosis nigricans, and sex as independent variables, had acceptable discrimination accuracy (AUROC 0.75) and 65.7% sensitivity (190/289 MetS cases). Its PPV was 36.5%, but 72.2% of false-positives (231/320) had one other metabolic abnormality beyond central adiposity. An alternative mixed process was also developed: first, all children with central adiposity and hypertension were considered as cases; secondly, a prediction model was developed on remaining normotensive children with central adiposity, yielding possibly-helpful discrimination (AUROC 0.67). This combined approach yielded higher sensitivity (75.4%) but lower PPV (30.7%) with more false-positives (n=493), of whom 57.0% (n=281) had one other metabolic abnormality beyond central adiposity.

Conclusions: It is possible to detect most undiagnosed MetS cases in school children and adolescents with non-invasive methods. Importantly, a large proportion of false-positive cases had metabolic abnormalities, so that the vast majority of youth identified by the model warranted medical follow-up.

P2-122**Insulin-like growth factor-1 and binding protein-3 in children with metabolic syndrome**

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Purpose: To examine the association of Insulin-like growth factor-1 (IGF-1) and binding protein-3 (IGFBP-3) with metabolic parameters of childhood obesity and assess its relationship with the presence of metabolic syndrome (MetS)

Methods: A cross-sectional study of total 307 children and adolescents referred for growth assessment was performed. Subjects were divided into three groups based on body mass index (BMI) percentile for age and gender. Anthropometric profiles and biochemical data were collected examining their association with IGF-1 and IGFBP-3.

Results: BMI was not significantly different in children with different quartile levels of IGF-1, IGFBP-3 and IGF-1/IGFBP-3 ratio. Alanine aminotransferase ($\beta=-0.01$, $p<0.01$), uric acid ($\beta=-0.13$, $p<0.01$) and total cholesterol ($\beta=-0.01$, $p=0.01$) were inversely associated with IGF-1 while not related to IGFBP-3 or IGF-1 to IGFBP-3 ratio. The prevalence of metabolic syndrome (MetS) was 11.2 % (63.64 % in males, 36.36 % in females) among children who were older than 10 years. IGF-1 was lower in children with MetS compared to ones without MetS (-1.51 ± 0.93 vs. -0.32 ± 1.10 , $p<0.01$) whereas showed no difference among groups subdivided by BMI. Low IGF-1 (OR: 0.24, 95 % CI: 0.09-0.63, $p<0.01$) and high IGFBP-3 (OR: 5.28, 95 % CI: 1.96-14.21, $p<0.01$) were found to be risk factors for MetS. In children with MetS, IGF-1, IGFBP-3, or IGF-1 to IGFBP-3 ratio had no significant association with individual components of MetS.

Conclusion: IGF-1 and IGFBP-3 may be another key factor related to metabolic parameter of obesity and the presence of MetS of youth. Elucidating the role of IGFs might help to understand its metabolic action in obesity related condition.

P2-123**Overweight, obesity and hypertension among adolescents – the impact of immigration and a acculturation**

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Aims: The migration from one cultural milieu to another has drastically increased cardiovascular risk factors and disease rates. We studied the prevalence of overweight and obesity, and hypertension among adolescents of Ethiopian origin who immigrated to Israel, as well as on Israeli born children of Ethiopian origin.

Methods: Adolescents aged 16-19 years, who were medically examined prior to mandatory military service in Israel between 1992 through 2016 were included. Participants of Ethiopian origin were classified into Israeli-born (N=15,793) and immigrants (N=23,487), and adolescents from families that were at least 3 generations in Israel served as controls (n=277,789). BMI was stratified by sex and divided to 6 groups: <17, 17.5-18.4, 18.5-19.9, 20.0-22.4, 22.5-24.9, >25.0 kg/m². Hypertensive-range blood pressure values adjusted for age, sex and height served as the outcome.

Results: The occurrence of hypertensive-range measurements increased with the length of residency in Israel: 7.3%, 10.6% and 14.4% in males who immigrated at ages 12-19, 6-12 and 0-6 years respectively, and 11.5%, 16.7% and 19.3% among females, respectively. Israeli-born Ethiopians had significantly higher risk for hypertensive range measurements at any BMI above 20 kg/m² compared to controls, after adjusting for socio-demographic and medical variables. Between 1992 and 2016, there was a 10-fold and 5-fold increase in overweight and obesity in males and females of Ethiopian origin respectively, compared to only 2-fold increase in the controls.

Conclusions: A pronounced increase in the prevalence of overweight and obesity among occurred in adolescents of Ethiopian origin occurred as well as an increased risk of elevated blood pressure compared to the Israeli population in every BMI group. The increase in the rates of obesity and of high blood pressure among adolescents of Ethiopian origin was according to year of immigration. These data are important in face of the waves of immigration that occur over recent years from developing countries to developed countries.

P2-124**Markers of bone metabolism in obese children and adolescents**

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Relevance: Evaluation of bone metabolism is a new scientific direction in the study of the long-term effects of childhood obesity.

Objective: To study markers of bone metabolism in children and adolescents with obesity.

Materials and Methods: 74 children with overweight and obesity in accordance with the WHO criteria and 25 healthy children with an average age of 15.4[11.6;19.2] years and 14.9[11.5;18.3] years, respectively, were surveyed. The levels of markers of osteogenesis (osteocalcin) and bone resorption (β -crosslaps) in the blood by ELISA were determined for all children. Statistical processing was performed using non-parametric methods.

Results: The level of osteocalcin in children with overweight and obesity corresponded to 37.3[12.3;62.3] ng/ml, significantly different from that in the group of practically healthy children (70.4[38.2;102.6], p<0.05). The level below the reference values was observed only in overweight and obese children (54.1%). The level of osteocalcin depended on the duration of the disease: <10 years - 63.0[41.0;85.0] ng/ml, >10 years - 23.7[5.1;42.3] ng/ml (p<0.01), which is also argued by the correlation coefficient (ρ =-0.507, p<0.001). There were no significant differences in the level of the marker, depending on the degree of overweight and the presence of obesity complications.

The level of β -crosslaps in patients with overweight and obesity was also significantly different from the level in healthy children: 0.73[0.24;1.22] ng/ml and 2.05[1.11;2.99] ng/ml, respectively (p<0.01). The level below the reference values was observed only in patients with obesity (2.7%). With an increase in the duration of obesity, the level of the marker decreased: <10 years - 1.00[0.45;1.55] ng/ml, >10 years - 0.53[0.13;0.93] ng/ml (p<0.01), this dependence is confirmed by the correlation coefficient (ρ =-0.464, p<0.001).

The results indicate a low level of bone metabolism in patients with obesity. The balance of bone formation and bone resorption in osteocalcin/ β -crosslaps ratio indicates a more significant inhibition of bone resorption in patients with obesity - 51.1[23.0;79.2] (in healthy children - 32.0[22.9;41.1]). However, as the duration of obesity increases, there is a simultaneous decrease in both bone formation and bone resorption: osteocalcin/ β -crosslaps with a disease duration of less than 10 years - 56.2[39.3;73.1], over 10 years - 43.2[27.2;59.2], p<0.01.

Conclusion: The results can explain the mechanism of formation of osteopenia in obesity in children.

P2-125**Clinical features and genetic analysis of childhood dyslipidemia**

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Objective: Dyslipidemia is a disease characterized by a genetic or multifactorial disorder of lipid and/or lipoprotein metabolism. Childhood dyslipidemia is a rare genetic metabolic disease that can cause serious cardiovascular disease and seriously endanger children's health.

Methods: We retrospectively analyzed the clinical data of 10 patients with dyslipidemia who were admitted to the Department of Endocrinology, Children's Hospital of Zhejiang University School of Medicine from August in 2009 to August in 2017. Seven probands and two of their parents underwent next generation sequencing.

Result: There were differences in the clinical phenotype of 10 probands, and four probands, P2 to P5, had strong pathogenic mutations.

1. Clinical phenotypes: (1) 10 cases of proband were from Zhejiang Province, there was 5 males and 5 females; (2) The median age of diagnosis is 4.7 years old; The age of onset clinical symptoms in hyperchylomicronemia were early; (3) The clinical manifestations were mostly xanthomas. Three of probands (P1, P2 and P10) were found that the creamy plasma appearance; (5) Among the clinical phenotypes, 5 cases were hypercholesterolemia, 4 cases were combined hyperlipidemia, and 1 case was hypertriglyceridemia. Two of them were low high density lipoproteinemia.

2. Molecular genetic results:LPL gene mutation was found in P2; the mutation of LDLR gene were found in P3. There were ABCG5 gene mutations in P4 and P5 (1 missense mutation and 1 nonsense mutation). There was a complex heterozygous mutation in P4, one is c.1166 G> A, a homozygous missense mutation of ABCG5, and both father and mother were heterozygous carriers. Another is heterozygous missense mutations of c.5002G>A and c.3121C>G of ABCA1. In P5, there was a homozygous nonsense mutation of c.751C>T in ABCG5. Both parents (normal phenotype) were heterozygous carriers. None of the above gene mutations were new mutations, and no pathogenic gene was found in P6 and P7.

3. Treatment and prognosis: They were all given dietary control of cholesterol intake, infants were controlled long-chain fatty acid intake. xanthoma of 2 sitosterolemia cases(P4 and P5) became larger. But after controlling animal and phytosterol intake simultaneously, the xanthoma has improved. No early-onset coronary heart disease has been found in these probands.

Conclusion: Children with dyslipidemia have diverse clinical phenotype and high genetic heterogeneity. Genetic testing can increase the accuracy of clinical diagnosis and contribute to early diagnosis and treatment of diseases. Sitosterolemia may be an important cause of hypercholesterolemia in China. The restriction of cholesterol and phytosterol intake should be suggested for sitosterolemia.

P2-126**Tracking Body Mass Index From Infancy into Childhood**

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Background and Aims: It has been postulated that the first 3 months of life are critical for programming of adult metabolic health. We investigated if Body Mass Index (BMI) and Fat Mass percentage (FM%) in early life tracks to 5 years of age and if feeding mode influences tracking.

Methods: In 268 term born, healthy infants from the Sophia Pluto cohort (161 boys), BMI was determined at 3 and 6 months, 2 and 5 years of age. FM% was measured at 3 and 6 months by PEA POD and at 2 and 5 years by DEXA.

BMI and FM% were divided in quartiles. Odds ratio (OR) of remaining in the same quartile over time was determined with logistic regression models.

Feeding mode was defined as exclusively breastfed if children had breast milk until at least 3 months and as exclusively formula fed if children started formula before 1 month.

Results: Median BMI increased from 15.94 kg/m² at 3 months to 16.62 kg/m² at 6 months and decreased to 15.64 kg/m² and 15.32 kg/m² at 2 and 5 years, resp.

From 3 months to 2 years, BMI tracked in all quartiles: OR for tracking in the lowest quartile was 4.33 ($p<0.001$), in second 1.68 ($p=0.046$), in third 2.55 ($p<0.001$) and in highest 7.07 ($p<0.001$). Tracking remained present until 5 years in 3 quartiles, with OR in the lowest quartile of 6.56 ($p=0.011$), in third 6.40 ($p=0.013$) and in highest 7.23 ($p=0.007$).

Median FM% increased from 22.9% to 24.1% between 3 and 6 months and decreased to 16.7% and 13.7% at 2 and 5 years, resp.

From 3 months to 2 and 5 years FM% tracked in the highest quartile: OR 2.18 ($p=0.010$) and 9.10 ($p=0.005$), resp. From 6 months to 2 years FM% tracked in 3 quartiles: OR for tracking in the lowest quartile was 3.03 ($p<0.001$), in third 2.02 ($p=0.025$) and in highest 3.72 ($p<0.001$). FM% tracked from 6 months to 5 years in 3 quartiles: OR for tracking in the lowest quartile was 8.00 ($p=0.012$), in second 21.75 ($p=0.007$) and in highest 4.33 ($p=0.046$).

Tracking of BMI and FM% was not influenced by feeding mode.

Conclusions: Our data show that BMI and FM% track through infancy into early childhood up to 5 years of age, suggesting that body composition is determined in the first months of life, regardless of feeding mode.

P2-127**The bilirubin/triglycerides ratio predicts changes over time in glycated hemoglobin in prepubertal healthy children**

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Background: Low serum bilirubin and high serum triglycerides are independently associated with higher risk of developing metabolic syndrome. Both bilirubin and triglycerides can regulate insulin secretion and glucose uptake. This is a first longitudinal study in healthy children to associate bilirubin and the bilirubin/triglycerides ratio with metabolic markers.

Objectives: Analyze independent associations between bilirubin and the bilirubin/triglycerides ratio with insulin secretion and resistance and HbA1c in a cohort of healthy prepubertal children.

Subjects/Methods: A cohort of 246 apparently healthy prepubertal children (mean age 8.8 ± 1.7 years) was studied. Of those, 142 (58%) were reevaluated 4 years later (mean age 12.9 ± 1.8 years). Anthropometric (BMI, waist) and metabolic parameters (total bilirubin, triglycerides, glucose, insulin, HOMA-IR, HOMA-β and HbA1c in fasting blood samples) were assessed. Both bivariate correlations and independent associations by means of multiple linear regression analyses were performed.

Results: Total bilirubin was not associated with either HOMA-IR or HOMA-β, but it was independently associated with HbA1c, both at baseline ($\beta = -0.208$; $p<0.001$; $R^2=3.2\%$) and at follow-up ($\beta = -0.261$; $p<0.002$; $R^2=6.1\%$). Stronger independent associations were found between the bilirubin/triglycerides ratio and HbA1c, both at baseline ($\beta = -0.294$; $p<0.0001$; $R^2=9.4\%$) and at follow-up ($\beta = -0.276$; $p<0.001$; $R^2=9.2\%$).

Conclusions: Bilirubin and specifically the bilirubin/triglycerides ratio is in prepubertal healthy children independently associated with HbA1c. Our results also indicate that the bilirubin/triglycerides ratio can predict changes in glucose tolerance over time in healthy children.

P2-128**Is one year of diet and physical activity program for obese children enough to revert the metabolic disorders?**

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Objectives: To analyse clinical and laboratory characteristics of an obese pediatric population.

To assess their response to specific program consisting in modification of their nutritional habits and physical activity.

Material and Methods: Obese patients completed a year of group therapy with nutritional education and physical activity. We analysed at the beginning and after a year anthropometry and body composition by bioimpedance (Tanita 33 TB), blood pressure, insulin, glycaemia, lipids and adiponectin. Metabolic syndrome (MS) was diagnosed according to IDF. Information regarding nutritional habits and physical activity was obtained with questionnaire. Data was analysed with SPSS 19.

Results: 68 patients (54.4% women), mean age of 10,26 (+/- 2,89) years were admitted in the study, 46,4% in puberty, BMI of 27,56 (+/- 3,95), SD 4,24 (+/- 1,5). 10 patients were diagnosed of MS and 13 of steatosis.

After a year, mean age 11,5 (+/- 2,9) years, 70,6% in puberty, BMI of 27,65 kg/m², SD 3,58 (+/- 1,7). 14 % normal weight. 9 patients MS (66,6% male), and 5 of these from the beginning.

An improvement in the quality of mediterranean diet and health habits was observed. There was decrease in sedentary activities (hour/day): from 3,3(+/- 2) to 2,7 (+/- 1,7) (p<0,001) and increase in physical activity 2,5 hours/week (p<0,001).

We observed statistical significant improvement of SD of the BMI (p<0,0001), an increase in lean mass (Kg) from 36,03 (+/- 11,37) to 41,49 (+/- 13,17) (p<0,003) and reduction in percentage of lean mass from 37,38 (+/- 5,75) to 35,58 (+/- 10,19). However, global increase in waist circumference was noticed from 85,39 (+/- 10,19) to 87,51 (+/- 11,8) (p< 0,015).

There was reduction in levels of adiponectin from 9,51 (+/- 4,63) to 8,27 (+/- 4,72) (p<0,0001) and increase in basal glycemia from 93,03 (+/- 6,94) to 96,87 (+/- 9,47) (p<0,009), which is above 100 mg/dl in 30,9% of the children after a year of follow-up.

None of the patients with MS presented hypertension or diabetes. 3 of them had glucose intolerance but with normal OGTT after a year.

Despite a decrease in insulin levels after a year follow-up, they were still high.

HOMA and TG/C-HDL indexes decreased without significant statistical differences.

Conclusions: Basal glycemia was increase after intervention. The program is effective in achieving improvement of healthy habits and to reduce degree of obesity, although it has not accomplished a decrease in abdominal adipose tissue. One year of study has not been enough to revert completely MS.

P2-129**Characterization of Adherence to Follow-Up and Therapeutical Outcomes in a Large Cohort of 1300 Patients with Obesity Visited in a Specialized Tertiary Care Center**

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Background: Adherence to follow-up visits in children and adolescents with obesity is a key factor for successful therapeutic outcomes in these patients.

Objective: To analyze the adherence to scheduled visits and drop-out rate and the anthropometric, metabolic and behavioral outcomes as a result of an intervention program in a large cohort of children and adolescents with obesity.

Patients and Methods: A retrospective, observational study of 1300 patients with obesity (47.2% females; 53.3% prepubertal; 75.8% Caucasians; mean age: 10.46 ± 3.28 years, BMI: +4.01 ± 1.49 SDS) undergoing an intervention program based on nutritional counseling, physical activity and behavioral therapy was performed. Drop-out rate and time of follow-up, as well as changes in eating patterns and physical activity were recorded. Paired comparisons of BMI-SDS, blood glucose, uric acid, lipoprotein, triglyceride levels and HOMA index from baseline (**B**) to the end of follow-up (**E**) were made, with ethnicity, sex and pubertal status included as variables.

Results: Mean follow-up time was 1.59 ± 1.60 years with a 59.9% drop-out rate [11.2% after first evaluation and 32.5% after getting the results of complementary examinations (second visit)]. Drop-out rate was higher in males (χ^2 : 14.70; p<0.05), prepubertal children (χ^2 : 6.39; p<0.05) and Latino patients (χ^2 : 28.94; p<0.001) and highest in the first 6 months. Among those who abandoned follow-up, 84.1% showed no fulfillment of clinical recommendations in their previous visit, whereas 10.5% showed clinical improvement. BMI-SDS at **E** was +3.59 ± 1.87 SDS decreasing 0.37 ± 1.25 SDS from **B** (p<0.001), mainly in the first year, with partial recovery in the second year and later stabilization. The BMI-SDS decrease was greater in males (p<0.01) and prepubertal children (p<0.001).

Unscheduled eating, quick eating pace and lack of physical activity significantly decreased (all p<0.001) from **B** (prevalence 81.9%, 74.0% and 74.7%, respectively) to **E** (57.2%, 47.3% and 49.8%).

The metabolic profile at both **B** and **E** was available in 451 patients. Impaired glucose tolerance (IGT) prevalence decreased from 9.3% at **B** to 3.5% at **E** (p<0.001). HDL level increased whereas HOMA index, LDL, uric acid and triglyceride levels decreased from **B** to **E** (all p<0.01), with a significant correlation between the intensity of the decrease in BMI-SDS and that of each metabolic change (p<0.01).

Conclusions: Therapeutic outcomes in childhood and adolescent obesity is determined by follow-up adherence. Unfortunately, there is a high drop-out rate, particularly in the first 6 months.

P2-130

Severe Obesity – Much More than an Unhealthy Lifestyle

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Introduction: Pediatric obesity is an important public health problem. Exogenous obesity represents most cases; in some children, obesity is attributable to endocrine or genetic disorders. Genetic etiology should be considered in children with dysmorphic features, global developmental delay, early onset severe obesity (before 5 years), hyperphagia or severe obesity family history. Regardless of the etiology, treatment must begin with long-term lifestyle changes. Nevertheless, specific genetic causes may require additional treatment strategies.

Case Report: The authors describe a 15y.o. female adolescent, referred to the Pediatric Endocrinology department at age of 10 due obesity and high stature. Personal history of late pre-term delivery, birth weight and length appropriate for gestational age; normal psychomotor development. No family history of overweight; mid-parental target height of 165.5cm (z-score +0.36). History of abnormal weight and height gain from 1y.o.: weight significantly greater than the 97th percentile from 15 months and height greater than the 97th percentile from 3 years of age. Excluded hyperphagia and other symptoms. Physical examination showed signs of cushing syndrome, 86.9kg (z-score +5.26), 160.1cm (z-score +3.35), BMI of 33.9 kg/m² (z-score +3.95) and Tanner M3P4. The first laboratory tests revealed high insulin-like growth factor (IGF-1) levels, reduced leptin levels, marked hyperinsulinism and bone age 2.5 years advanced. The oral glucose tolerance test did not show complete suppression of somatotropin levels. The MRI revealed an enlarged adenohypophysis. Subsequent evaluations showed IGF-1 normalization, variable leptin levels and persisting marked hyperinsulinism. Serial neuroimaging exams were similar to the initial one. Because of maintained excessive ponderal gain, an obesity genetic testing panel was performed. Mutations in three genes were identified: melanocortin-4 receptor (MC4R) in heterozygosity; ghrelin (GHRL) in heterozygosity; and aquaporin 7 (AQP7) in homozygosity. The MC4R gene variant was identified in the father (no overweight).

Comments: The authors present a case of early onset severe non-syndromic obesity with mutations in three distinct genes. The MC4R mutations have been described as the main cause of genetic obesity. However, the detected variant does not explain *per se* this child obesity. Whereas GHRL and AQP7 mutations have been described as obesity risk factors, they cannot individually explain the observed condition. The authors suggest a possible synergistic effect of all three mutations as the underlying cause of this severe obesity. In vitro functional or animal studies may explain the pathogenicity of these mutations. Concluding, it is mandatory to always consider a genetic etiology in children with early onset severe obesity.

P2-131

Serum 25-hydroxyvitamin D Levels and Insulin Sensitivity Across Pubertal Stages in Obese Children

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Background: Decreased serum 25-hydroxyvitamin D (25-OHD) level has frequently been reported in obesity, a condition which is associated with insulin resistance. Insulin resistance was negatively associated with serum 25-OHD. Puberty is the period with altered insulin sensitivity. Previous studies showed conflicting results of the variation of serum 25-OHD levels across pubertal stages. However, data on serum 25-OHD levels across pubertal stages in obese children are limited.

Objective: To determine serum 25-OHD levels and insulin sensitivity across pubertal stages in obese children

Methods: There were 230 obese children, aged 11.4 (2.5) years, enrolled. All children underwent an OGTT and had serum 25-OHD, Ca, P and intact parathyroid hormone (iPTH) levels measured. All children were classified into 3 groups of puberty; Tanner I (N = 62), Tanner II & III (N = 88) and Tanner IV & V (N = 80). Insulin sensitivity indices [whole body insulin sensitivity index (WBISI) and homeostatic model assessment of insulin resistance (HOMA-IR)] and β-cell function indices [HOMA-β and insulino-genic index (IGI)] were calculated from serum glucose and insulin levels derived during the OGTT.

Results: Mean (SD) 25-OHD level was 26 (7) ng/mL. Despite being less obese with advanced stages of puberty [BMI Z-scores for Tanner I, II & III and IV & V: 2.9 (2.4, 3.7), 2.4 (2.1, 3.0) and 2.2 (1.8, 2.5), respectively, *p* <0.001], serum 25-OHD were progressively decreased [30 (6), 26 (7) and 23 (6) ng/mL, *p* <0.001]. Differences in calcitropic parameters were also observed among the 3 groups [iPTH: 31 (25, 38), 35 (29, 46) and 40 (32, 53) pg/mL, *p* <0.001; Ca: 9.6 (9.4, 9.8), 9.6 (9.2, 9.8) and 9.3 (9.0, 9.6) mg/dL, *p* = 0.002]. Changes of insulin sensitivity did not follow the same pattern as that of serum 25-OHD with maximum insulin resistance observed during Tanner stages II & III [WBISI: 3.0 (1.9, 4.8), 2.1 (1.6, 3.3) and 3.3 (2.0, 4.3), *p* <0.001; HOMA-IR: 2.5 (1.5, 3.9), 3.1 (2.1, 4.5) and 2.6 (1.8, 3.8), *p* = 0.021]. After adjustment for age, sex and BMI Z-score, puberty was negatively associated with serum 25-OHD. However, insulin sensitivity and β-cell function indices were not associated with serum 25-OHD.

Conclusion: Progressive decrease in serum 25-OHD level was observed with more advanced stage of puberty in obese children and did not follow the same pattern as that of insulin sensitivity. Therefore, the changes of serum 25-OHD were unlikely related to insulin sensitivity.

P2-132**Association Between Tsh And Metabolic Syndrome In Obese Children And Adolescents**

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Introduction: Hyperthyrotropinemia is common in patients with obesity and has been hypothesized that high TSH could be associated with an adverse metabolic profile. Few studies have been performed in pediatric population and the results are controversial.

Objective: Aim of the study was to evaluate the association between TSH and metabolic syndrome (MS) in a large group of obese children and adolescents.

Patients and Methods: 1402 obese patients (median age 9.7 (2.2-17.8) years, 646 Male) were included in this retrospective analysis. All patients were euthyroid or affected by mild isolated hyperthyrotropinemia with TSH between 4.5-10 µU/ml and normal fT4. Waist circumference, blood pressure, fasting glycemia, insulin and lipids were measured in all subjects. MS was defined according to the IDEFICS criteria in 2-10 years patients and IDF criteria in patients ≥10 years. Homeostatic Model Assessment (HOMA index, glycemia(mmol/L) x insulin (mU/L)/22.5) was calculated as insulin resistance index. Patients were subdivided into 3 groups according to their TSH level: normal-low TSH (group A, 930 patients, TSH: ≥ 0.5 - < 2.5 µU/ml), normal-high TSH (group B, 432 patients, TSH: ≥ 2.5 - < 4.5 µU/ml), mild isolated hyperthyrotropinemia (group C, 40 patients, TSH: ≥ 4.5 - < 10 µU/ml).

Results: The overall prevalence of mild isolated hyperthyrotropinemia was 2.9%.

Median BMI, WC, and fT4 were similar among the 3 groups. The prevalence of MS was higher in patients with hyperthyrotropinemia versus euthyroid patients ($p \leq 0.01$), but no difference was found between normal-low and normal-high TSH patients (group A 10.4%, group B 11.6%, group C 25%). Among the components of MS, the prevalence of hypertension was higher in patients with hyperthyrotropinemia versus euthyroid patients ($p \leq 0.01$), but no difference was found between normal-low and normal-high TSH patients (group A 14.3%, group B 18.1%, group C 36.1%). The prevalence of patients with abnormal HOMA was higher even in normal-high versus normal-low TSH patients ($p < 0.001$, group A 39.6%, group B 49%, group C 65%).

The results were similar when the 742 patients of 2-10 years were separately analysed.

Conclusions: In our large cohort of obese children and adolescents, high TSH was associated with higher prevalence of MS, regardless of their body status and fT4 levels. These results confirm the correlation between TSH and the metabolic profile, even in children <10 years. Further studies are needed to define if TSH could be involved in the pathogenesis of cardiovascular complications in obesity.

P2-133**Primary hyperlipidemia in children: experience of 11 years from a referral center in Vietnam**

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Primary hyperlipidemia is a group of diseases caused by genetic defects involved in the synthesis, transport and metabolism of lipoproteins.

Objectives: our aim is to describe the clinical, biochemistry and imagine characteristics of primary hyperlipidemia and to review outcome of management for patients with primary hyperlipidemia.

Subjects and Methods: this is case series study including 59 patients from 51 unrelated families. These cases had longitudinal monitoring from 1/2006 to 8/2017.

Results: Among 59 cases, 18 patients (30.5%) from 15 unrelated families had hypercholesterolemia, 1 case had homozygous familial hypercholesterolemia; 34 patients (57.6%) from 31 unrelated families had hypertriglyceridemia; 7 patients from 7 unrelated families (11.9%) had with mixed hyperlipidemia. Only patients with hypercholesterolemia and hypertriglyceridemia had xanthoma. Hepatomegaly and splenomegaly were recognized only in patients with hypertriglyceridemia and mixed hyperlipidemia patients. Early cardiovascular complications are only seen in patients with hypercholesterolemia, acute pancreatitis were seen in both hypertriglyceridemic and mixed hyperlipidemic patients. The serum total cholesterol level was 12.68 ± 4.9 mmol/l and LDL-cholesterol level was 10.98 ± 4.22 in hypercholesterolemia group. The serum triglyceride level was 41.9 ± 63.79 mmol/l and total cholesterol level was 7.37 ± 8.2 mmol/l in hypertriglyceridemia group. The serum total cholesterol level was 6.28 ± 1.11 mmol/l and triglyceride level was 15.6 ± 5.16 mmol/l in mixed hyperlipidemia group. Best outcome of therapeutic goal was seen in patients with mixed hyperlipidemias, followed by patients with hypertriglyceridemia, and patients with hypercholesterolemia.

Conclusions: clinical manifestations in patients with primary hyperlipidemia are likely to be missed diagnosis. Screening for hyperlipidemia in high-risk infants should be developed to help preventing cardiovascular disease complications, as well as acute pancreatitis.

P2-134**Tumor Necrosis Factor Alpha in Metabolic Syndrome Development In Children**

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Background: Tumor necrosis factor alpha (cachexin) is a cell signaling cytokine involved in systemic inflammation process. It is produced chiefly by activated macrophages, although it can be produced by many other cell types such as CD4+ lymphocytes, NK cells, neutrophils, mast cells, eosinophils, and neurons. The

primary role of TNF alpha is the regulation of immune cells. TNF, being an endogenous pyrogen, is able to induce fever, apoptotic cell death, and inflammation, inhibit tumorigenesis and viral replication, and respond to sepsis via IL1 & IL6 producing cells. TNF alpha is connected with a body mass decrease and cachexia development.

The aim of the study: The correlation of TNF alpha levels with elements of metabolic syndrome in obese children.

Patients and Methods: TNF alpha in serum was measured in 462 obese and 60 healthy children (ELISA). In all patients, BMI was calculated, blood pressure was measured, and lipidogram, insulin, and glucose level were estimated in peripheral blood samples (ELISA Abbott). HOMA-IR was calculated as a marker of insulin resistance. The results were statistically analyzed using Statistica 10.

Results: TNF-alpha levels were statistically significantly lower ($5,41 \pm 1,09$ pg/ml) in children with obesity in comparison to the control group ($7,89 \pm 1,02$ pg/ml) ($p < 0,02$). A negative correlation with the BMI, HOMA-IR, LDL cholesterol, and triglyceride levels was observed. A low level of TNF alpha was observed in children with elevated systolic blood pressure over 95 percentile.

Conclusion: The low TNF alpha level is connected with development of metabolic syndrome in children.

and paternal grandmother, both of whom carry a maternally derived deletion with clinically normal phenotypes. In the second case, there are two affected sibs fulfilling diagnostic criteria for typical PWS as well as one suspected cousin with milder cognitive impairment. The karyotype analysis of the patients and their mother showed the seemingly cytogenetic abnormality-45,XX,rob(15;15)(q10;q10) due to a translocation involving maternal chromosome 15 and hence effective maternal uniparental disomy for the PWS region. We provide the genetic findings of the probands' pedigrees in the aspects of clinical evaluations and conclude molecular cytogenetic mechanism analysis of Prader-Willi Syndrome, so as to a better prenatal diagnosis and corresponding genetic counseling in such families, especially when estimating the recurrence risks in families.

P2-136

Insulin resistance and impaired glucose tolerance in overweight/obese adolescents attending an obesity clinic in Belgium

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Background: Obesity is a global epidemic and major health concern. Studies on insulin resistance and glucose abnormalities in European overweight/obese adolescents are rare.

Aim: To study prevalence of insulin resistance, impaired glucose tolerance and type 2 diabetes mellitus in a cohort of overweight/obese adolescents. To determine correlations between patient characteristics and biochemical parameters of glucose homeostasis.

Method: An oral glucose tolerance tests (OGTT) was performed in 156 overweight or obese adolescents (82 girls/ 74 boys, age 12 to 17 years) as part of the initial medical evaluation in our obesity clinic during a period of 4 years. The mean body mass index (BMI) was $28,9 \text{ kg/m}^2$. According to the International Obesity Task Force (IOTF) BMI cut-offs, 10 % of patients were classified 'overweight', 49 % 'class I', 31 % 'class II' and 10 % 'class III obesity'. Acanthosis nigricans was present in 19% of patients and a familial history of diabetes was reported in 58%. Fasting blood glucose, fasting insulinemia, peak insulinemia and blood glucose level 120 minutes after ingestion of glucose were determined during OGTT. The HOMA-IR score was calculated. Statistical analysis was performed to determine correlations between patient characteristics and the above-mentioned biochemical parameters of glucose homeostasis.

Results: Most of the patients (86%) had a peak insulinemia during OGTT higher than 800 pmol/L . Even more patients (90%) had an HOMA-IR score above 2.9. The 4 patients with HOMA-IR score under 1.4, had a peak insulinemia of 730 pmol/L or higher and one of these (with HOMA-IR score of 0.5) had a peak insulinemia of 6900 pmol/L .

Only 1 patient (0.6 %) had blood glucose level above 200 mg/dL 120 minutes after administration of glucose (type 2 diabetes mellitus), while 21 patients (13%) had blood glucose level above 140 mg/dL (impaired glucose tolerance). Impaired fasting glucose was detected in 19 patients (12%).

P2-135

Clinical and Cytogenetic Analysis on Two Chinese Familial Cases of Prader-Willi Syndrome with Multiple Affected Patients

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Prader-Willi Syndrome (PWS [MIM 176270]) is a rare neurogenetic disorder mapping to the chromosome 15q11-q13 domain, which results from the genetic and epigenetic function deficiency of genomic imprinting of paternal alleles. It is characterized by neonatal hypotonia with following childhood obesity, hyperphagia, developmental delay and short stature, hypogonadism, cognitive impairment, and behavioral problems. PWS is generally sporadic that occurs in about 1 in 10 000 to 30 000 live births. The majority of individuals have the paternal deletion of proximal 15q, secondary to a chromosome 15 reciprocal translocation, inversion, uniparental maternal disomy 15, or imprinting defects. Familial inheritance of PWS has been reported but shows a rare familial simultaneous occurrence. We describe here the first reported familial cases in China of demonstrative findings of Prader-Willi syndrome and carry out family studies to analyze the different underlying cytogenetics mechanisms. In the first case, two affected sibs present the characteristic features with severe neonatal hypotony, hyporeflexia, little cry at birth and hypogonadism seen in PWS. They both harbour a paternally transmitted 417 kilobase pairs (kbp) [array15q11.2(24,963,375-25,380,656)x1] deletion in 15q11.2-q13 of the PWS imprinting region. The submicrodeletion, verified by single nucleotide polymorphism (SNP) array and methylation-specific MLPA (MS-MLPA), passes through the paternal line from the patients' father

A significant correlation was found between BMI and fasting insulinemia and between BMI and peak insulinemia. We also found correlations between BMI and age, BMI and familial history of diabetes mellitus, fasting insulinemia and peak insulinemia, and finally between peak insulinemia and blood glucose level after 120 minutes.

Conclusion: Although a very high percentage of overweight/obese adolescents has insulin resistance, only a minority of adolescents has glucose intolerance of impaired fasting glucose. Type 2 diabetes mellitus is rarely observed in the overweight/obese adolescents we see. Further studies are necessary to explore this.

P2-137

Clinical characteristics and response to growth hormone treatment in patients with Prader-Willi Syndrome

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Introduction and aim: Prader-Willi syndrome(PWS), is a genetic disorder caused by the absence of paternal genes located on chromosome 15q11.2-q13. In this multi-central study; patients with PWS were followed for 2 years. Initial clinical and laboratory findings, growth hormone(GH) treatments and their responses were evaluated.

Patients and Methods: 54 patients from 10 pediatric endocrine centers were involved and data was evaluated retrospectively from the national data system. Complaints at admission, initial and follow up anthropometric measurements, thyroid and gonadal functions were noted. Clinical and laboratory findings of the patients who had growth hormone treatment and their responses were recorded.

Results: Fifty%(n=27) of the patients were boys. Mean age at admission was 2.7 ± 3.2 years, 96,3%(n=52) of the patients were prepubertal. The most frequent complaint was hypotonia %55.6(n=30).

Cryptorchidism and micropenis were observed in 66%(n=18) and 14,8%(n=4) of the boys. At admission mean height, weight and BMI SDS of the patients were -1.20 ± 1.25 , 0.4 ± 2.26 , and 1.08 ± 2.58 respectively. Short stature was observed in 22,2%(n=12). BMI was $>2SD$ in 44%(n=24), $<-2SD$ in 16,7%(n=9). Age was positively correlated with BMI SDS ($r=0.84$, $p<0.001$). With increasing age obesity as a complaint at admission increased($p<0.019$). With decreasing age poor nutrition as an initial complaint increased($p<0.035$). Preterm delivery, SGA and LGA were reported in %16,7(n=9), 38,9 % (n=9), and 1,8%(n=1) of the patients. In all of the patients except 2, PWS was diagnosed genetically. Paternal microdeletion, uniparental disomy, and imprinting defects were detected in 64.8%(n=35), 11.1%(n=6), and 5.5%(n=3) of the patients. Fifteen %(n=8) of patients were diagnosed only by methylation abnormality. Central hypothyroidism, primary hypothyroidism, central adrenal insufficiency, hypogonadotropic and hypergonadotropic hypogonadism were observed in 28.3%(n=15), 11,3%(n=6), 3,7%(n=2), 3,7%(n=2), and 1,8 %(n=1) of the patients respectively. The most frequent behavioral problem was learning disability [55.8%(n=19)]. Scoliosis was the most observed skeleton problem [%22.2(n=12)]. Obstructive sleep apnea was reported in 42.6%(n=23). GH treatment was started in 46.2%(n=22) at the mean age of 4.72 ± 2.7 years and with a mean dose of 0.025 ± 0.005 mg/day. After 1 year of treatment although there was no statistical difference in BMI SDS, height SDS($p<0.001$) increased.

Conclusion: Clinical findings differ according to age. Feeding difficulties are observed in younger patients, obesity is observed in older children. Growth hormone treatment although increased height SDS it didn't effect BMI in one year. Longer growth hormone treatment durations are needed to draw definite conclusions.

P2-138

A Rapid Instrument for Diagnosis and Screening of Pediatric Obesity and its Complications: The Neck Circumference

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Objectives: Pediatric obesity (PO) leads in adulthood to chronic high-risk pathologies, if not adequately identified and addressed. The anthropometric methods for evaluating PO have well-described limits. One of the most recently proposed indexes to better locate and evaluate PO is the neck circumference (NC). We have verified the relationship between NC, body mass index (BMI), waist circumference (WC) and some laboratory parameters, with the aim of defining the validity of NC as an instrument for screening PO and its hepato-metabolic complications (HMC).

Methods: Our study was performed involving 100 (62 boys, 38 girls, age 5-16 years) obese children (BMI z-score 2.44 ± 0.35) recruited at our pediatric endocrinology service of "Santa Maria della Speranza" Hospital, Battipaglia (Italy). Everyone performed: weight/height measurement, WC, NC, arterial pressure [systolic (SBP) and diastolic (DBP)]; laboratory determination of blood glucose, insulin, ALT, AST, GGT, cholesterol, HDL, LDL, triglycerides, ESR, RCP; abdominal ultrasound examination to establish the presence/absence of bright liver (hepatic steatosis). BMI,

HOMA index, CC / CV ratio have been obtained. Spearman's correlation coefficient was calculated between NC, WC, BMI and laboratory values.

Results: Alla obese children had a NC > 95th percentiles for sex and age (cut off: 30.5 - 46.5 cm), mean value 35.97 ± 4.2 cm. NC correlated significantly with BMI ($R = 0.66832$, $P = 0.0001$), WC ($R = 0.69944$ $P = 0.00005$) and blood uric acid (UA) values ($R = 0.53685$, $P = 0.04777$). UA was > 6.5 mg/dL in 30% of our studied sample. No correlation ($p > 0.05$) between NC and inflammatory indexes, transaminases, HOMA index, lipid profile, SBP/DBP, hepatic steatosis was found.

Conclusions: This study of our series shows that NC could be used as an alternative to BMI and WC, to identify PO and related HMC risk factors.

P2-139

The prevalence of elevated blood pressure and hypertension in Korean adolescents, based on the guidelines of Endocrine Society and American Academy of Pediatrics

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Purpose: Childhood obesity epidemic leads an interest of pre-stage of hypertension; higher/elevated blood pressure (BP) status which BP numbers are lower than the criteria for diagnosing hypertension. In 2017, the clinical practice guidelines for pediatric BP management were published separately by Endocrine Society (ES) and American Academy of Pediatrics (AAP). The aims of this study are to evaluate the prevalence of elevated blood pressure (EBP) including hypertension (HTN) and the difference of those according to the guidelines in Korean adolescents.

Methods: We analyzed data of 1166 adolescents aged 13-17 years (male/female 611/555) from the Korea National Health and Nutrition Examination Survey (2014-2016). BP group were categorized as normal, EBP and HTN according to each guideline and prevalence of EBP and HTN were analyzed and compared. In ES guideline BP of $>90^{\text{th}}$ percentile to $<95^{\text{th}}$ percentile or $>120/80$ is prehypertension, BP $\geq 95^{\text{th}}$ percentile to $<99^{\text{th}}$ percentile + 5 mm Hg is stage 1 HTN and BP $\geq 99^{\text{th}}$ percentile + 5 mm Hg is stage 2 HTN. In AAP guideline, elevated BP is defined as $>120/80$ to $129/80$ mm Hg, Stage 1 HTN is $130/80$ to $139/89$ mm Hg and Stage 2 HTN is BP $\geq 140/90$ mm Hg

Results: The average age was 14.97 years and body mass index (BMI) z-score was 0.06 and 0.08 in boys and girls, respectively. 23% of boys and 22% of girls were overweight including obesity. 11.8% of boys and 31.5% of girls were central obesity defined by waist circumference (WC) above 90th percentile for gender and age. Systolic BP was 111.99 and 106.13 mmHg, and diastolic BP was 67.39 and 66.63mmHg in boys and girls, respectively. BP was positively correlated with BMI z-score and WC percentile.

The prevalence of EBP was 36.5% vs. 25.2% according to ES and AAP, respectively in boys and 25.1% vs. 10.1% in girls. HTN prevalence was 23.7% vs. 12.3% in boys and 18.9% vs. 5.4% in girls. The prevalence of EBP and HTN were different by the guideline, in each gender. Prior to diagnosis of hypertension, 5% to 13% of adolescents could initiate life style intervention by EBP criteria.

Conclusion: One in three or four of Korean adolescents has increased blood pressure and the prevalence of EBP and HTN were different according to ES and AAP guideline. Early therapeutic interventions such as life style modification including diet and physical activity should be started in adolescents with EBP.

P2-140

PEDOBESITY: Development of Intelligent Multi-level Information Systems and Specialized Artificial Intelligence Algorithms for Personalized Management of Obesity in Childhood and Adolescence

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Background: Obesity in childhood and adolescence represents a major health problem of our century. In Greece, more than 30-35% of children and adolescents are currently overweight or obese.

Objective: To evaluate and further develop the 'National Registry for the Prevention and Management of Overweight and Obesity in Childhood and Adolescence' in order to provide personalized intervention programs for overweight and obese children and adolescents using intelligent information systems and support systems.

Methodology: The project is part of the Operational Program "Competitiveness, Entrepreneurship & Innovation, EPAnEK 2014-2020" (project code: T1EDK-01386, MIS: 5030543, Acronym: PEDOBESITY), which is co-funded by Greece and the European Union, and represents continuation of the Program "Development of a National System for the Prevention and Management of Overweight and Obesity in Childhood and Adolescence in Greece". The main innovative actions include: (1) Collection and analysis of clinical, hematological, biochemical, endocrinological and genetic data of overweight and obese children and adolescents; (2) Detection of polymorphisms associated with obesity, diabetes

type 2, antioxidant ability and body mass index; (3) Development of a specific obesity-risk algorithm by linking each genotype to the patient's data, as well as published information on how it affects body weight at clinical or genetic level; (4) Development of interconnected online and mobile applications to integrate the ecosystem of applications for childhood obesity. Applications will include development and expansion of the Electronic Health File (EHR) of the "National Registry for the Prevention and Management of Overweight and Obesity in Childhood and Adolescence", Patient Access Subsystem and Online Support, as well as mobile application for children, adolescents and their parents; (5) The development of an intelligent data management platform (in full interoperability with the "National Registry for the Prevention and Management of Overweight and Obesity in Childhood and Adolescence") using the innovative methodology of Fuzzy Cognitive Maps and modeling techniques from medical data analysis in order to provide personalized treatment guidelines.

Results: Our goal is to reduce overweight and obesity rates in Greece by at least 20% within 5 years following implementation of the project.

Conclusions: These research actions are expected to play an important role in the effective management of childhood obesity.

P2-141

Metabolic syndrome risk assessment in Indian children and adolescents

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Objective: To assess the risk of metabolic syndrome (MS) in children and adolescents as per the recommendation based on the age and sex-specific reference curves for Waist Circumference (WC) for Indian children by Khadilkar et al.

Study design: A total of 370 children (200 girls, 170 boys) aged 6 to 18years coming for regular checkups to our center from January 2016 to March 2019 with WC >70th percentile were enrolled. All children were assessed for metabolic syndrome risk factors with respect to BMI, BP measurements, and levels of fasting triglycerides, high-density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL), and fasting plasma glucose were recorded for all patients.

Prevalence rates of MS in the pediatric age group vary depending on the criteria used. The International Diabetes Federation's (IDF) definition of MS in children has been divided according to the following age groups (6-10 years, 10-16 years, and 16+ years). For those aged 6 to <10yr, though MS cannot be diagnosed but further measurements were made in children with a family history of metabolic syndrome (MS), type 2 diabetes mellitus (T2DM), dyslipidemia, cardiovascular disease, hypertension and/or obesity.

Results: As per IDF definition, 64 out of 240 (26.66%) children in the 10 to 18 year age group met the criteria for pediatric metabolic syndrome.

Age group	10 to <16yr (n=217)	16-18yr (n=23)
Percentage meeting the IDF criteria	23.5%	56.52%

Those aged 6 to <10years with a family history of MS, T2DM, dyslipidemia, cardiovascular disease, hypertension and/or obesity were also evaluated for metabolic syndrome. Eighteen out of 130 children (13.84%) met the criteria for metabolic syndrome as per IDF definition in this age group.

Children were also evaluated for MS as per the modified definition proposed by NCEP/ATPIII. As per this definition, 63 out of 158 (39.8%) children in the age group of 12-18yr met the criteria for pediatric metabolic syndrome.

Gender	Males (n=78)	Females (n=80)
Percentage meeting the NECP criteria	34.61%	45%

Conclusion: Overall, 39.8% and 26.66% children met the NCEP/ATPIII & IDF criteria respectively. The low incidence of MS with IDF definition may be due to the cut-off value used for blood pressure as systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg for all age groups.

The WC percentiles proposed for Indian children are useful in identifying children with metabolic syndrome. Early detection and management is vital in halting the progression of this syndrome pathway in children.

P2-142

Vitamin D status in obese children and its relationship with leptin and adiponectin

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Introduction: obesity is a major health problem worldwide and its incidence is increasing annually. Adipose tissue produces and regulates many hormones and cytokines which have relationship with obesity comorbidity. Serum level of vitamin D has been previously reported to have a negative relationship with obesity.

Objective: To evaluate the relationship between vitamin D status and leptin, adiponectin, lipid profile and Insulin resistance in obese children.

Material & Method: A total of 61 children including 32 obese (BMI > 95th percentile according to CDC curves for sex and age) and 29 normal weight subjects, aged 4-17 year, were randomly enrolled in this study. After clinical evaluation and anthropometric measurements, fasting serum level of vitamin D, leptin and adiponectin were assessed using ELISA method. Fasting plasma level of total cholesterol, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), Triglyceride (TG), glucose and insulin were measured with colorimetric kits and homeostasis model assessment of insulin resistance (HOMA-IR) was calculated.

Result: In our study there was not any significant difference of vitamin D level between obese and normal-weight children. However, in obese children the levels of serum leptin, total cholesterol, LDL-C, TG and HOMA-IR were significantly higher than control group, while HDL-C did not show any significant difference. Adiponectin in obese cases was significantly lower than that in control group. There was a significant negative correlation between leptin and vitamin D in control group but the same result was not observed in obese group.

Conclusion: Vitamin D level is not influenced by obesity and it is negatively correlated with leptin regardless of weight. There is no correlation between Vitamin D level with adiponectin, lipid profile and insulin resistance.

Fetal, Neonatal Endocrinology and Metabolism (to Include Hypoglycaemia)

P2-143

Two Siblings with Tyrosinaemia Type 1 and Transient Hyperinsulinaemic Hypoglycaemia

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Introduction: Tyrosinaemia type 1 (TT1) is a rare autosomal recessively inherited disorder of tyrosine metabolism leading to accumulation of tyrosine and its metabolites in liver, kidney and central nervous system. TT1 is a heterogeneous disorder with a broad spectrum of clinical manifestations. Hypoglycaemia is common, especially in the acute phase of the disease due to liver failure and reduced hepatic clearance of insulin. However, confirmed cases of hyperinsulinaemic hypoglycaemia have also been recently described.

Case: We describe the case of two siblings with TT1 who were born to consanguineous parents. Both siblings were found to be homozygous for pathogenic variant c.192G>Tp. (Gln64His) in fumarylacetoacetate hydrolase (FAH) gene which they inherited from their parents who were heterozygous carriers of the same mutation. The proband was a female child diagnosed with TT1 following elevated phenylalanine on newborn screening and liver failure. She was also found to be hypoglycaemic in the neonatal period. Hypoglycaemia screen confirmed the diagnosis of hyperinsulinaemic hypoglycaemia which was well controlled on a combination of diazoxide and chlorothiazide. Her treatment was discontinued after 8 months with normal blood glucose (BG) control and appropriate fasting duration since then.

Her brother was screened and diagnosed with TT1 at birth due to positive family history. He also manifested with neonatal hypoglycaemia. Diagnostic workup revealed detectable insulin

at the time of hypoglycaemia and inability to mobilise ketones and fatty acids confirming the diagnosis of hyperinsulinaemic hypoglycaemia. Therefore, he was commenced on diazoxide and chlorothiazide which normalised his BG. His treatment was discontinued after 6 months with age-appropriate fast tolerance and no further hypoglycaemia off medication.

Conclusion: We describe two siblings with TT1 and acute liver dysfunction who had transient hyperinsulinaemic hypoglycaemia in the neonatal period. Both siblings were successfully treated with diazoxide (3mg/kg/day) and chlorothiazide (7mg/kg/day) and treatment was gradually withdrawn after 8 and 6 months, respectively.

Although histological abnormalities of the pancreas including beta cell hyperplasia are well documented, the exact mechanism of excessive insulin secretion in TT1 is not well understood. It may be related to the accumulation of toxic metabolites in the target organs including pancreas. Therefore, in patients with TT1 and persistent hypoglycaemia, it is important to exclude hyperinsulinism which is usually transient and can be successfully treated with diazoxide and chlorothiazide. Further studies are required to determine which factors contribute to excessive insulin secretion in patients with TT1.

P2-144

Glucagon therapy in preterm infants with hyperinsulinemic hypoglycaemia

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Background: The treatment of preterms with hyperinsulinemic hypoglycaemia is a well-known challenge. One of the difficulties of the therapy is the excessive application of intravenous fluids to compensate high carbohydrate needs. There are various drug alternatives such as glucagon, diazoxide or somatostatin analogues apart from intravenous glucose application.

Hypothesis: Intravenous or continuous subcutaneous glucagon therapy are suitable alternatives to stabilize blood sugar levels without causing complications in preterm infants.

Methods: A two-centre retrospective data analysis was initiated. Data of patients with the diagnosis of prematurity and hyperinsulinemic hypoglycaemia with glucagon therapy between 2008 and 2019 were analysed.

Results: Medical records from 762 preterm patients were evaluated. 9 preterms were treated with glucagon aside from intravenous glucose therapy. Continuous treatment was applied either intravenously or subcutaneously (off-label). Start of therapy was between day 3 and 25 after birth. Amount of carbohydrate intake scaled between 9 and 24.4 g/kg/d. All 9 patients showed a rapid stabilization of blood sugar levels in the first 48 hours of glucagon therapy. Median increase of blood sugar levels ranged between 9 and 140%. Treatment lasted between 4 and 39 days with a glucagon dose range of 12.9 to 34 µg/kg/h. 2 patients were treated

intravenously. 3 patients were treated intravenously and through time subcutaneously. 4 other patients were treated intravenously or subcutaneously with glucagon, additional oral diazoxide and/or subcutaneous octreotide. Due to low solubility of glucagon high infusion rates and periodic exchange of the subcutaneous catheter were necessary to prevent catheter obstruction. Hyponatraemia or thrombocytopenia as known side effects of glucagon therapy were not detected. One patient treated subcutaneously showed a cutaneous abscess. Uncomplicated relief puncture showed a good curative treatment.

Discussion: In our cohort, glucagon therapy was rarely initiated. Based on rare experiences glucagon seems to be an adequate medication for rapid stabilisation of low blood sugar levels for hyperinsulinemic hypoglycaemic preterms. It can be used to bridge the time until diazoxide as a potential long term medication shows effectiveness. Intravenous or subcutaneous application of the dose spectrum mentioned shows good effects and tolerance. Continuous peripheral intravenous and subcutaneous application of glucagon seem to be advantageous methods to prevent hyperhydration and edema through excessive intravenous glucose application. Through subcutaneous therapy a continuous glucagon application is guaranteed even if peripheral glucose treatment is interrupted. Off-Label subcutaneous glucagon therapy should be used more often leading to establishment of standards for glucagon therapy in preterm.

P2-145

Neonatal Hypo-Ketotic Hypoglycemia Secondary to Transient Hyperinsulinism. Diazoxide Responsiveness and Experience with Fasting Test After Treatment Withdrawal

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Introduction: Transient hyperinsulinism is described in neonates with stress factors (*intrauterine growth restriction (IUGR)*, large for gestational age (LGA), perinatal asphyxia, infants of diabetic mother etc.). Recognition and early treatment is prioritary to avoid neurological morbidity related with recurrent hypoglycemia.

Objective: Describe the incidence of transient hyperinsulinism. Clinical characterization and treatment response in neonates with hypoglycemia due to hyperinsulinism (monogenic forms excluded) admitted to a tertiary hospital NICU from 2015 to 2018.

Materials: Prospective cohort study. Newborns > 7 days of age, with diagnostic criteria for hyperinsulinism: non ketotic hypoglycemia with detectable insulin levels, reduced free fatty acids, glucose infusion rate > 10mg/kg/min, and positive response to glucagon test).

Results: Of 3525 patients admitted, 0.8% (N = 28) presented hypoglycemia secondary to transient hyperinsulinism. Ratio male/female: 57/43%. Ethnic group: 57% Caucasian, 15% Asian, 4%

Hispanic American, 10% African and 4% Arabians. 78% were preterm babies (median 33 weeks of gestational age), 71% birth weight or height <-1.6 SD (median height of -1.9 SD and -2.1 SD). The median diagnosis age was 26 days (IQR 11-29 days), with enteral feeding exclusively. Median blood glucose at diagnosis was 1.94mmol/L (IQR 1.66-2.28mmol/L), 3 patients (10%) were infants of diabetic mother and 40% presented acidosis with cord blood pH<7.20.

85% received diazoxide treatment (dose ranged between 5-10mg/kg/day), presenting as most prevalent side effects hypertrichosis (91%) and edema (25%).

Diazoxide median treatment duration was 91 days (IQR 43-109). The response was positive in 100%, with a fasting test performed on an outpatient basis, with glycemia > 60mg / dl after 10 hours of fasting after treatment withdrawal.

Comparing preterm with term neonates, no significant differences were found regarding diazoxide treatment duration, maximum carbohydrate intake or resolution age.

Molecular study was carried out through guided NGS in 70% of patients. No mutations were found so far in genes involving monogenic hyperinsulinism (*ABCC8, KCNJ11, HNF4A, GLUD1, HADH, SLC16A1, GCK, UCP2, HNF1A, AKT2, INSR, CACNA1D*), however, probably pathogenic variants were found in other candidate genes.

Conclusions: Transient hyperinsulinism is a prevalent entity to be considered in neonates with risk factors. In our series, term newborns presented transient hyperinsulinism (21% of patients) and newborns with weight and/or height appropriate for gestational age (28%). Low dose diazoxide treatment is effective. The fasting test could be useful for safe treatment withdrawal when resolution is suspected.

P2-146

Severe Neonatal Hyperparathyroidism Due to a Novel Homozygous Mutation of the Calcium-Sensing Receptor (CaSR)

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Homozygous loss-of-function mutations of the calcium-sensing receptor gene (*CaSR*) are associated with neonatal severe hyperparathyroidism (NSHPT), a life-threatening condition with a challenging treatment approach.

We report a 7-day-old-female infant who was admitted to our Pediatric Department due to poor sucking. On examination she was lethargic and hypotonic. Laboratory evaluation revealed

extreme hypercalcemia of 23.54 mg/dL (N: 7.6–10.4) with normal albumin levels, low phosphorus concentration of 2.16 mg/dL (N: 4.0–6.5), and extremely high PTH of 568 pg/mL (N: 18.4–80.1). The biochemical findings indicated NSHPT. Treatment was initiated with hyperhydration and IV bisphosphonate and calcitonin for the first 24 hours, which reduced calcium levels to the normal range within days. Cinacalcet was thereafter initiated at a dose of 0.35 mg/kg per day with an increase up to 7.5 mg/kg per day. Skeletal survey revealed bone deformities of the femur with evidence of growth-plate injury and severe osteopenia. Molecular analysis of *CaSR* identified a novel homozygous mutation: c.281G>A (p.Gly94Glu). The parents are first cousins and were heterozygous; the mother had had elevated PTH levels in the past that normalized with vitamin D therapy, and the paternal grandmother had undergone parathyroidectomy (PTX). Despite normal calcium levels, our patient's PTH remained elevated and there was progressive bone disease. Therefore, at 9 weeks of age, a total PTX with auto-transplantation of one gland in the thigh was performed. After PTX, the PTH levels decreased and hypocalcemia gradually evolved, necessitating initiation of oral calcium and alfalcacidol. This case report demonstrates the challenges of treating NSHPT and indicates that the therapeutic goal must be to reduce serum levels of both calcium and PTH, as elevated PTH by itself can cause severe bone deformities. Finally, because *CaSR* has specialized roles in the brain and bone cells, even with correction of serum calcium and PTH levels, these patients remain at risk for neurocognitive and skeletal defects.

P2-147

A rare cause of pediatric hypoglycemia in a boy: a malignant insulinoma

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Insulinoma is a rare neuroendocrine tumor, usually benign, but can be life-threatening in causing hypoglycemic accidents. It presents in individuals aged between 8 and 82 years and can occur sporadically or constitute a part of multiple endocrine neoplasia type 1 (MEN-1). The nonspecific symptoms and small size of these tumors led to difficulties of diagnosis and localization.

Here we describe the case of a 11-year-old boy, who came to our attention for a 1-month history of confusion, amnesia and diplopia, occurring during severe hypoglycemia. His past medical history revealed three simple febrile seizure in the first two years of life.

At presentation, patient was vitally and hemodynamically stable. Cardiovascular, respiratory, gastrointestinal and neurological examinations were normal.

Initial laboratory investigations showed low blood glucose (48 mg/dL) and high blood insulin levels (62.74 µIU/ml) with detectable C-peptide values. Complete blood count, hepatic, renal, serum electrolytes, thyroid, parathyroid and prolactin profiles were normal. Urinary sample was negative for ketones. During hospitalization, glucose monitoring showed fasting low glucose levels

(32 mg/dl). As very low serum glucose levels were associated with inappropriately high serum insulin and detectable C-peptide levels, the diagnosis of endogenous hyperinsulinism was made.

In view of hypoglycemic symptoms and possible insulinoma, patient underwent to radiological investigations. The abdominal contrast-enhanced MR showed a 40 mm, well-demarcated lesion within the head of pancreas associated with mild dilatation of pancreatic duct and retropancreatic lymphadenopathy (34x10 mm). No distant metastasis was identified.

After diagnosis confirmation, a continuous infusion of 10% glucose was started to maintain normal serum glucose levels. The patient underwent duodenocephalopancreatectomy after two weeks.

The definitive histological examination revealed a neuroendocrine tumor, well differentiated (NET-G2 sec. WHO 2010) of 4,5 cm infiltrating vascular and perineural districts, with metastasis in 2 pancreatic-duodenal lymph nodes among the 9 that had been surgically removed. Immunohistochemical staining was positive for synaptophysin (replicative index Ki67:10%). The most recent abdominal revaluation did not reveal any recurrence of disease and currently the patient is in good conditions and with normal glycemic levels.

Insulinoma in childhood is generally rare. Even if the vast majority of them (90%) are benign, a small percentage (10%) may have a malignant behavior. Clinicians must maintain a high index of suspicion for insulinoma in the presence of young patients with frequent hypoglycemic symptoms because early recognition is important to ensure proper surgical treatment and prevent serious adverse neurological consequences.

P2-148

Neonatal Hyperglycemia

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Hyperglycemia in newborns is most common in premature infants. At present, in clinical practice, the attitude towards this type of metabolic disorders is not well defined and controversial.

Objective: To determine the feasibility of prescribing insulin for hyperglycemia in premature newborns.

Patients and methods. We observed 68 newborns with a birth weight of 1326 ± 119.8 g and a gestational age of 29 ± 1.1 weeks. In the early neonatal period, hyperglycemia was observed in all children (9.3 - 10.2 mmol / l; glycosuria - 0.5%).

Determination of glucose in the blood was carried out by the method of Glucose oxidase.

Results: All children had such problems with adaptation as respiratory distress syndrome and cerebral pathology. 45 children received insulin injections. 23 children did not receive insulin treatment. None of the newborns had symptoms of hypoglycemia. In the insulin group, the caloric value increased from 38 ± 30 to 68 ± 19 kcal / kg / day. In the group where the newborns did not receive any treatment with insulin, the caloric value was 39 ± 21 kcal / kg / day. It took the insulin group 10 ± 5 days to reach normal body weight at birth. While the group that did not receive insulin treatment, it took 11 ± 6 days. At the end of the neonatal period, hyperglycemia disappeared. But in 16 children (9 from the insulin

group and 7 from the other group), intraventricular hemorrhage was noted with degrees II and III. All newborns were transferred to spontaneous breathing at 10 ± 5 days after birth. Thus, we found no evidence of differences in the observed groups.

Conclusions: In preterm infants with very low birth weight, hyperglycemia can be considered a transitional state. The appointment of insulin inappropriate.

P2-149

Clinical and genetic characteristics of patients with hyperinsulinaemic hypoglycaemia diagnosed and treated at a tertiary endocrine center, a part of the ENDO-ERN

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Background: Hyperinsulinaemic hypoglycaemia (HH) is a clinically and genetically heterogeneous group of disorders characterized by persistent hypoglycaemia due to inappropriate insulin secretion from the pancreatic β -cell.

Aim: The objective was to analyze the demographic, clinical and genetic characteristics of patients with HH, diagnosed and/or treated at a tertiary endocrine center, part of the European reference network on rare endocrine conditions (ENDO-ERN).

Material and Methods: The medical records of a total of 13 patients with congenital HH (9 persistent, 3 transient, and 1 syndromic cases) were retrospectively reviewed. Data about their demographic, clinical and biochemical characteristics were collected. Genetic testing was performed in all patients with persistent and syndromic hyperinsulinism.

Results: Ten children (76.7%) were males and almost 2/3 of the patients (61.5%) presented at birth with hyperinsulinism. Four patients (30.8%) were born large for gestational age and the most common clinical manifestations at presentation were neuroglycopenic symptoms. *ABCC8* and *GLUD1* gene mutations were identified in 44.4% of the nine children with persistent hyperinsulinism. Of the three *ABCC8* cases, one had homozygous p.(Gly92Asp) mutation, one was compound heterozygous p.(I60N)/p.(G1555V) and one was heterozygous for a dominant mutation p.(E1507K). The patient with syndromic hyperinsulinism was diagnosed with Beckwith-Wiedemann syndrome due to a loss of heterozygosity for the maternal allele resulting in loss of methylation in KvDMR and gain of methylation in H19 DMR. Eleven children (84.6%) were diazoxide responsive and two patients received octreotide treatment. Patients with detected mutations were diagnosed earlier, with lower blood glucose levels and required higher doses of diazoxide compared to children without a genetic diagnosis. More than 92% (12/13) of the children with HH had normal neurological development, excluding one patient with expressive language problems due to diagnostic and treatment delay.

Conclusion: The majority of hyperinsulinaemic patients have no identifiable mutations, suggesting the role of other genetic and environmental mechanisms. Since most of the patients present soon after birth, early recognition and prompt treatment are vital in preventing permanent brain damage.

P2-150

Relations Of O2 Supplementation To Blood Serum Insulin-Like Growth Factor-II / Insulin-Like Growth Factor-Binding Protein-3 Ratios in the Not-Life-Threatened Human Newborn; Role of Oral-Enteral Caloric Intake Beyond Axillary Temperature

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Introduction: Oral/enteral caloric intake (KOE) insufficiency may accompany human newborn (NWB) respiratory derangements. We detected axillary temperature(TEMP) relations to NWB blood serum Insulin-like Growth Factor-II(IG2)-blood serum Insulin-like Growth Factor-Binding Protein-3(IB3) ratios(IG2/IB3R). Here we evaluate the TEMP-independent relevance of birth gestational age(GA) and KOE to relationships of O2 supplementation in respiratory gases(O2S) with IG2/IB3R in not-life-threatened NWBs.

Methods: NWBs with any among total parenteral nutrition, parenteral nutrition other than dextrose, blood component transfusion, postnatal corticosteroid treatment, therapeutic hypothermia, life-threatening disease, diabetes mellitus(DM), endocrine diagnosis out of DM, malformation, and mother with DM were excluded. Each of 78 included NWBs had complete data availability for 1) same-day records at one of the first 5 postnatal days(x), 5 days after x(y) and 10 days after x(z) of postnatal age(PNA, unit:day), TEMP(unit: $^{\circ}$ C), total caloric intake(KT) and KOE (KT, KOE, unit: kcal/kg body weight/24hrs), pulse oximetry(SpO2, unit:%), O2S, IG2 and IB3 RIA measurements(unit:uM/dl), and for 2) gender(SEX), GA(unit:complete week; range=28-42), GA<36(preterm birth, n=46), BW(unit:g; range=1200-4150), BW<=10.th centile for GA(SGA). We calculated: 1) IG2/IB3R (IG2 through chronologically corresponding IB3), 2) averages over x-y-z times(i.e., (x+y+z)/3), for TEMP(TEMPM;range=36.1-37.0), K(KM), KOE(KOEM), SpO2(SpO2M; range=87.3-100.0) and IG2/IB3(IG2/IB3M), and 3) percents of KOEM over KM (i.e., (KOEM through KM)x100, KOEM%KM; range=24.5-100.0). IG2/IB3M normal score according to van der Waerden(IG2/IB3M-NS) resulted near-normally distributed. Multiple Linear Regression(MLR) was used for analyses(MLR computations; male

SEX, SGA, O2S at x(O2Sx), condition absent=0, condition present=1)(n; male SEX, 43; SGA, 20; O2Sx, 22).

Results: Partial correlation coefficient (pcc) for partial correlation between O2Sx and outcome IG2/IB3M-NS was significant in MLR models bearing, as predictors, 1) SEX, SGA, PNA, TEMPM, KM and O2Sx (pcc, r₂: .423, p=.0002) or 2) SEX, SGA, PNA, TEMPM, KM, O2Sx and SpO2M (pcc, r₂: .403, p=.0004) but not 3) GA and/or KOEM%KM in addition to SEX, SGA, PNA, TEMPM, KM and O2Sx or 4) GA and/or KOEM%KM in addition to SEX, SGA, PNA, TEMPM, KM, O2Sx and SpO2M (MLR R₂: .337-.465, always significant).

Conclusions: GA and/or KOEM%KM may be involved in SO2x - IG2/IB3M-NS relations after control for TEMPM in addition to SEX, SGA, PNA, TEMPM, KM, and SpO2M.

P2-151

Refractory Hyperinsulinaemic Hypoglycaemia in Beckwith-Wiedemann Syndrome due to Imprinting Centre 1 Gain of Methylation: Severity Discordant to Genotype

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Introduction: Beckwith-Wiedemann syndrome (BWS) is an overgrowth syndrome caused by multiple epigenetic/genetic changes affecting imprinted genes in 11p15.5 region. Phenotypic expression is variable. Hyperinsulinaemic hypoglycaemia is common (30-60%). Persistent, severe, refractory cases are usually associated with 11p15 paternal uniparental disomy, particularly the rare context of a coexisting paternal inactivating K_{ATP} channel variant. Those cases may have large, focal pancreatic lesions. In BWS due to other molecular defects, hypoglycaemia usually resolves within days. Persistent cases are usually diazoxide-responsive.

Case: BWS, suspected antenatally, was confirmed postnatally in a female (35 weeks gestation, unaffected parents, spontaneous non-consanguineous conception, no family history of hypoglycaemia). She had macroglossia, but no exomphalos, lateralised overgrowth or placental mesenchymal hyperplasia (cardinal Beckwith-Wiedemann spectrum, BWSp features). Of suggestive features, she was macrosomic with diastasis recti, umbilical hernia; without polyhydramnios, nephromegaly, ear creases/pits or facial naevus simplex.

The molecular defect was gain of methylation at H19/IGF2 intergenic differentially methylated region (IGDMR), known as Imprinting Centre 1 (IC1). This genotype accounts for 5% of BWS. Wilms' tumour risk is high (24%).

Unexpected for genotype, she had severe, congenital hyperinsulinism (CHI) refractory to medical therapy (diazoxide, octreotide). There were no detected ABCC8 or KCNJ11 variants. This genotype would not predict focal disease. At 11 weeks, a subtotal pancreatectomy (80-85%) was performed. In this context, reducing endocrine tissue mass may suffice. Histology was atypical for focal or diffuse CHI, with large, numerous islets as previously observed in BWS.

Complications included catheter-related bloodstream infections and thromboses. Macroglossia exacerbated feeding difficulties.

CHI was again refractory to octreotide. Sirolimus exacerbated transaminitis and anaemia. The brief trial was ceased at the onset of a sepsis episode. [18F]-DOPA PET/CT scan did not indicate the unlikely scenario of ectopic disease. Further resection to equivalent of at least 95% pancreatectomy was performed two weeks after the initial resection. Exocrine pancreatic insufficiency resulted, however CHI persisted.

After further medical support including Lanreotide from 8 months, she was discharged at 9 months.

At 14 months, she continues monthly Lanreotide. She is orally fed with pancreatic enzyme and fat-soluble vitamin supplements. Tumour surveillance is negative. There is no evident neurocognitive impairment. Macroglossia has impeded expressive language development. She has mixed sleep-disordered breathing. Tongue-reduction surgery is planned.

Conclusion: The CHI severity was discordant to that previously reported for this BWS genotype. Although clinical heterogeneity has been described in the different genotype of IC2 hypomethylation (accounts for 50% of BWS), those cases were diazoxide-responsive.

P2-152

Congenital Hyperinsulinism due to Compound Heterozygous mutations in ABCC8 fully responsive to Diazoxide therapy

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Background: Congenital Hyperinsulinism (CHI), a condition characterised by dysregulation of insulin secretion from the pancreatic beta cells, remains one of the most common causes of hyperinsulinaemic, hypoketotic hypoglycaemia in the newborn period. Mutations in ABCC8 and KCNJ11 constitute the majority of genetic forms of CHI. Biallelic inactivating mutations (homozygous or compound heterozygous) in ABCC8 and KCNJ11 are known to result in severe, diffuse, diaxoxide unresponsive hypoglycaemia. We report a neonate with CHI due to compound heterozygous mutations in ABCC8 and completely responsive to diazoxide.

Case: A term macrosomic male baby, birth weight 4.81 kg, born to non-consanguineous parents, presented on day 1 of life with severe and persistent hypoglycaemia. Apart from polyhydramnios during the antenatal period, the pregnancy was otherwise uneventful. Normoglycaemia (blood glucose >3.5 mmol/L) was achieved with a peak glucose infusion rate (GIR) of 20 mg/kg/minute. The hypoglycaemia screen showed an inappropriately raised plasma insulin 50.4 mIU/L when the plasma blood glucose level was 0.5 mmol/L with suppressed free fatty acids and beta-hydroxybutyrate, confirming the diagnosis of CHI. Following a normal baseline echocardiogram, diazoxide was commenced initially at a dose 5 mg/kg/day in conjunction with chlorothiazide. The intravenous fluids were weaned and normoglycaemia was sustained with a high dose of diazoxide (15 mg/kg/day) and enteral nasogastric formula feeding 150 ml/kg/day. Molecular genetic analysis of the proband confirmed biallelic ABCC8 mutations: missense c.4079C>T (pathogenic) and splicing c.4122+1G>A (pathogenic) variants inherited from the unaffected father and mother respectively. The proband is currently 4 months old and continues to show a sustained response to his current diazoxide dose 7.5 mg/kg/day and formula feeding (4 hourly) via naso-gastric tube due to vomiting on oral feeds. The MRI brain showed a deep medullary sinus thrombosis which is being managed conservatively. The investigations to look for the causes of persistent vomiting on oral feeds are currently underway.

Discussion: Rapid genetic analysis is integral in the management of CHI as a tool to identify patients who may not respond to standard therapy of diazoxide, and those who may need F-DOPA PET scan and possible pancreatectomy. Although the majority of biallelic ABCC8 mutations cause diazoxide unresponsive CHI, very rarely they can show a complete response to diazoxide treatment. The molecular interaction behind this is currently unclear. An accurate assessment to diazoxide responsiveness is therefore warranted before considering alternative therapies.

GH and IGFs

P2-153

Criteria for first-year growth response to growth hormone treatment in prepubertal children with growth hormone deficiency: do they predict final height outcome?

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Background/aim: Several criteria for the first year growth response (FYGR) to growth hormone (GH) treatment have been proposed. We explored which FYGR criteria predict best the final height outcome after GH treatment in prepubertal children with GH deficiency (GHD).

Methods: Height data of 129 GHD children (83 boys) treated with GH for at least 4 consecutive years with at least 1 year before pubertal onset, were retrieved from the Belgian GH Registry. The FYGR parameters were: (1) increase in height (ΔHt) SDS, (2) height velocity (HV) SDS, (3) ΔHV (cm/year), (4) index of responsiveness (IoR) in KIGS prediction models, (5) first-year HV SDS based on the KIGS expected HV curve (HV KIGS SDS), (6) near final adult height (nFAH) prediction after first-year GH treatment. Poor final height outcome (PFHO) criteria were: (1) nFAH SDS <-2.0, (2) nFAH SDS minus midparental height SDS <-1.3, (3) total ΔHt SDS <1.0. ROC curve analyses were performed to define the optimal cut-off for FYGR parameters. Only ROC curves with an area under the curve (AUC) of more than 70% were further analyzed.

Results: Twenty two, 10 and 12 % of the children had respectively a nFAH SDS <-2, nFAH SDS minus midparental height SDS <-1.3, and total ΔHt SDS <1. The AUC's ranged between 73 and 85 %. The highest AUC was found for first-year ΔHt SDS to predict total ΔHt SDS <1, and predicted nFAH SDS to predict nFAH SDS <-2. Most currently used FYGR criteria had a low specificity and sensitivity to detect a PFHO at their standard cut-off values. ROC curve analyses revealed that to obtain a desired specificity of 95% the cut-off value (and sensitivity) of the FYGR parameters were: ΔHt SDS < 0.35 (40%), HV SDS < -0.85 (43%), ΔHV < 1.3 cm/year (36%), IoR <-1.57 (17%), and HV KIGS SDS <-0.83 (40%) to predict total ΔHt SDS <1; predicted nFAH SDS (with GH peak) < -1.94 (25%), and predicted nFAH SDS (without GH peak) < -2.02

(25%) to predict nFAH SDS < -2. At these cut-offs with 95% specificity the amount of correctly diagnosed poor final responders equals the amount of false positives.

Conclusion: First-year growth response criteria for GH treatment perform poorly as tests to predict a poor final height outcome.

P2-154

Determinants of the peak GH response of the glucagon stimulation test in slowly growing children

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Background/Aim: Currently, the minimum of the GH peak (pGH) to GH provocative stimuli, including the glucagon stimulation test (GST), has been arbitrary set in children at 7 µg/L, irrespective of gender and age. Several doses (fixed or per bodyweight) and ways of administration (IM or SC) of glucagon are being used in daily practice. This retrospective study explores the influence of gender, age, and adiposity on the pGH after a maximally effective glucagon stimulation (0.1 mg/kg (max 2 mg) IM) and the relationship between blood glucose (BG) and GH dynamics.

Methods: Auxological and hormonal data of 84 (49 male) slowly growing (growth velocity < P25) children and adolescents (age < 18 years), who underwent a GST (in 11 subjects after priming) in 2013-2014 in two University Hospitals were retrieved. In 26 of them an insulin tolerance test (ITT) had been performed before and in 3 after the GST. In all children, GH was measured by the IDS-iSYS assay.

Results: Median(range) age was 8.1 (0.8-17.5) years and height SDS was -2.7 (-6.3 - 0.8). Median pGH after GST was similar in males and females, but significantly ($p < 0.005$) higher than after ITT in non-primed subjects (8.4 (1.2-16.3) vs 4.4 (0.9-6.9) µg/L), in whom pGH correlated significantly with age ($r = 0.29$, $p < 0.05$) and serum IGF-1 ($r = 0.41$; $p < 0.005$). In 28 (33 %) of the 84 children pGH after GST was lower than 7 µg/L. BG during GST became lower than 50 mg/dL in 30 (36 %) subjects. BG nadir correlated with age ($r = 0.31$; $p < 0.005$), weight SDS ($r = 0.23$; $p < 0.05$) and basal BG ($r = 0.48$; $p < 0.005$), but not with the pGH.

Conclusion: The GST, when performed as a second test, in a dose of 0.1 mg/kg bodyweight, is more powerful in releasing GH than the ITT. The pGH after GST is dependent on age in a non-primed condition, but independent of gender or weight status. We propose to use the GST as a first line GH test to avoid the need for a second ITT test, given its higher potency, independency of weight status and low risk of hypoglycemia.

P2-155

First Reported Egyptian Sibs with The Rare Laron Syndrome

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Laron's syndrome, or Laron-type dwarfism, is an autosomal recessive disorder characterized by an insensitivity to growth hormone. There are exceptionally low levels of insulin-like growth factor (IGF-1) caused by homozygous or compound heterozygous mutation in the growth hormone receptor gene. It causes severe short stature and can be treated with injections of recombinant IGF-1. Laron syndrome is a rare disorder. About 350 people have been diagnosed with the condition worldwide. The majority of reported cases of Laron syndrome have been in people with Semitic origin.

Here, we are presenting the first reported Egyptian sibs affected with this rare disorder. Two boys born to first cousins, nine and seven years old presenting with abnormally severe short stature (dwarfism), prominent forehead, depressed nasal bridge, underdevelopment of mandible and micropenis. Development and mentality were normal.

Several studies are now investigating the role Cyproheptadine HCl (CyproH) as a treatment for this disorder. CyproH is an appetite-stimulating drug and while it was prescribed for a patient with growth hormone insensitivity syndrome (GHIS) for increasing appetite, his height growth was surprisingly increased. Our patients are now on CyproH treatment; 0.25 mg/kg/24 hours as an alternative to recombinant IGF-1 which is very expensive, and interestingly, a marked increase in height is noticed.

P2-156

Growth hormone monotherapy versus Combined GH and LHRH analog in 2 sisters with short stature, early pubertal development, and advanced bone age (BA)

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Introduction: There is still a debate on the effect of combined treatment with growth hormone (GH) and a luteinizing hormone-releasing hormone (LHRH) analog versus GH alone on final adult height in children with idiopathic short stature (ISS) and those who have early pubertal development at a short height.

Case Report: We studied two sisters with a history of familial short stature, early puberty and advanced bone age at presentation. Both of them presented to the endocrine clinic with the same presentation at the same age, in two different times. (R) presented with breasts Tanner 3 and was menstruating for 9 months. She was treated with GH monotherapy (0.05 mg/kg/day) for 2 years until her final adult height (FAHt). (D) presented at the same age with breast Tanner 3 and menstruated once. She received combined GH and LHRH-a therapy and still on treatment. (Table)

Age at Presentation	(R) 10.5 years old	(D) 10.5 years old
Breast development	T3	T3
Menarche	9 months	1 month
HtSDS 1	0.34	-1.5
MPhSDS	-1.5	-1.5
BMISDS1	1.47	0.85
BA	11.5	12
Hormones	FSH : 3.39 IU/L LH : 4.87 IU/L Estradiol : 182 pmol/L	FSH : 4.70 IU/L LH : 3 IU/L Estradiol : 277 pmol/L
Intervention	GH therapy	combined
Age 2	11.5	11.5
HtSDS2	0.06	-0.54
BMISDS2	1.72	0.79
GV/y 1	5cm	6.9
GVSDS	-0.7	0.9
BA	13.5 y	12
Age 3	12.5	---
HtSDS3	-0.77	----
BMISDS3	1.5	----
GV/y 2	2.4cm/y	----
BA	15y	---
End adult Ht* (cm)	152	157.8 (predicted)
HtSDS	-1.68	-0.89

At presentation, pubertal stage and BA were equal in both sisters. However, (D) was significantly shorter (difference 1.84 SDS). After a year of follow up on different therapies (D) showed significant improvement in HtSDS, GV and GVSDS (LHRH-a + GH effect) in comparison to her sister (R) who received GH monotherapy, with a change in HtSDS = +1 in (D) versus -0.28 in (R). The combined therapy resulted in a deceleration of bone aging that increased the potential of FAHt. (R) Received GH for 2years stopped therapy when she achieved final adult height (152cm, SDS -0.73) in comparison to her MPhSDS -1.5. The predicted FAHt for D, who was shorter at presentation, proved that she will be taller than her sister (157.8 cm, -0.89)

Conclusion: In these sisters with advanced BA and early puberty, the combined LHRH-a + GH therapy proved to be more beneficial for height growth compared to GH monotherapy.

P2-157

Long-term follow-up of three patients with isolated growth hormone deficiency type IA with sustained growth response to rhGH

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Background: Isolated growth hormone deficiency type IA (IGHD IA) is described in families with homozygous *GH1* deletions that arise from unequal recombination and crossing over within the GH gene cluster during meiosis. Patients with IGHD

IA show early and severe growth failure and tend to develop antibodies upon treatment with recombinant human growth hormone (rhGH).

Aims: To present the follow-up of three patients with IGHD IA treated with rhGH.

Methods: *GH1* gene was analysed by PCR.

Results: Three female patients were included in the study. All patients were of Avars origin and were born from consanguineous marriages. Two girls were second cousins. Me of birth weight was +0.2 SD, Me of birth length +0.5 SD. The patients had typical features of congenital GHD: frontal bossing, doll face, acromicria and truncal obesity. Low height velocity was detected at the age of 3-6 months. The first evaluation showed severe growth retardation: -6.4 SD (1.9 year, case 1), -4.9 SD (1 year, case 2), -7.3 SD (1.6 year, case 3) with normal BMI. IGF-I level was undetectable (less than 3 ng/ml); TSH, fT4, prolactin and cortisol levels were normal. DNA analysis revealed homozygous deletion of *GH1* gene in all three patients. Diagnosis of IGHD IA was established. rhGH therapy ("Rastan", Russia) was started at dose 0.033 mg/kg per day. Height and HV were measured at baseline and every 6 months during the treatment period (from 1 to 5 years). IGF-I levels were monitored during therapy and were in the normal limits according to age and sex. HV increased after 2-4 months of rhGH, during the first year of therapy median of growth velocity was 20 cm/year. Over 2 years of treatment (cases 1 and 3), patients' height increased from 60.8 ± 2.5 to 93.9 ± 3.7 cm, with an increase in height SDS from -6.85 ± 0.45 to -0.18 ± 0.05 . After 5years' follow-up of patient 3, Δ height SD was +7 and growth velocity was 10.2 cm/year.

Conclusions: GH resistance is not a uniform feature of IGHD IA. The sustained GH response observed in the above cases may be related to the patients' genotypes and/or type of rhGH preparation.

P2-158**Clinical and genetic characteristics of eleven Korean patients with hypochondroplasia and outcomes of growth hormone therapy**

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Hypochondroplasia (HCH) is an autosomal dominant inherited skeletal dysplasia with abnormal growth pattern and inadequate pubertal growth spurt. Achondroplasia and HCH have many similar phenotype, however, HCH show the mildest phenotype among *FGFR3*-associated skeletal dysplasia, and the radiologic findings are usually so subtle. We investigated to evaluate clue for the hypochondroplasia, and clinical and genetic characteristics of eleven Korean patients with HCH. We also demonstrate the growth promoting effect of a recombinant growth hormone (rGH) treatment in three patients with HCH.

Clinical data were obtained from the medical records of eleven patients with HCH from ten unrelated families. The data included height, brachydactyly, genu varum, lumbar lordosis, generalized laxity, limitation of elbow extension, macrocephaly, and mental retardation. Radiological evaluations were performed. The *FGFR3* mutational status was studied by *FGFR3* whole exome sequencing. Effectiveness of rGH therapy was analyzed in three patients.

All patients showed brachydactyly. Six patients showed definitely short stature (less than -2 SDS), but other five patients did not show significant short stature (mean Height SDS -2.54 vs -1.68 respectively). Genu varum was observed in six patients. Radiographic features revealed failure of widening of the inferior lumbar interpedicular distance, metaphyseal flaring, squared and short ilia, flattened acetabular roofs, and elongation of distal fibula with varied frequencies. The *FGFR3* gene analysis revealed one novel mutation (p.Thr330Ile) in one patient and four known mutations were detected in nine patients (p.Lys650Asn, p.Lys650Thr and p.Ser84Leu were found in each 3 proband, and p.Asn540Lys in the other six probands). Three patients who received rGH, the mean height SDS increased by average 0.274 per year during the study period. The mean SDS of baseline IGF-1 value was -0.275 before rGH treatment and 0.630 ± 0.848 during the last year of observation.

Detailed investigations of radiologic features of HCH are important because of a mild or sometimes an absent phenotype. *FGFR3* whole exon sequencing is a useful method because HCH has variable mutation positions. rGH treatment durably improves growth in children with HCH. Improvement of body disproportion should be studied in the further study.

Key words: hypochondroplasia, *FGFR3* mutation, clinical characteristics and recombinant growth hormone therapy.

P2-159**Growth hormone treatment adherence in Latin American patients: 2-year real world data from the easypod™ connect eHealth platform**

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The easypod™ injection device allows automatic recording and transmission of adherence data from patients receiving recombinant human growth hormone (r-hGH; Saizen) to treat growth disorders. Through the easypod™ connect platform, healthcare professionals can access transmitted data and gain insights into adherence patterns. This analysis aimed to evaluate real-world adherence to r-hGH therapy administered via easypod™ at 1, 3, 6, 12 and 24 months, plus overall data at 48 months in Latin American (LATAM) patients.

Data were downloaded on 15th February 2019 from 4,530 patients transmitting to easypod™ connect in nine LATAM countries (Argentina, Brazil, Chile, Colombia, El Salvador, Guatemala, Mexico, Nicaragua and Peru). The period of recorded data varied, according to individual's treatment length. Patient adherence (categorised as high [$\geq 85\%$], intermediate [$>56\%-84\%$] or low [$\leq 56\%$]) was calculated as mg Saizen injected vs mg Saizen prescribed. Only data after the 10th injection registered on easypod™ were analysed. Puberty cut-off points were 10 years for girls and 12 years for boys.

In total, 4,459 patients recorded >10 injections. Overall, there were 2,719 patients (61.0 %), 1,267 (28.4%) and 473 (10.6%) in the high, intermediate and low-adherence categories, respectively. A decrease in the proportion of patients in the high adherence category was observed over time, however, at month 24, 57.5% patients (422 of 734) were still in the high adherence category. At month 24, more females than males were in the high-adherence group (179 of 297 [60.3%] vs 243 of 437 [55.6%]), while a slightly higher proportion of younger patients recorded high-adherence data compared to older patients (95 of 159 [59.7%] vs 327 of 575 [56.9%]). The overall mean number of data transmissions was 5.10 [SD 9.87] and 4.87 [SD 9.39] in the high and intermediate-adherence categories respectively, compared with 2.52 [SD 3.45] in the low adherence category.

This is an update of the real-world analysis conducted in LATAM patients using easypod™ connect, and evaluates 2-years of adherence data. Similarly, more girls than boys were in the high adherence group, while younger patients showed slightly higher adherence. Through our validated method of recording adherence, we can address an unmet need in r-hGH therapy. Patient/caregiver engagement via data transmission has the unique potential of providing information about data patterns of individual patients and may act as a foundation for care improvement.

Metabolic Outcome in Adolescents with Growth Hormone Deficiency During Transition Phase

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Background: It is well known that GH deficiency (GHD) in adulthood is associated with detrimental cardiovascular (CV) effects. Although data are controversial, adolescents with childhood-onset GHD (COGHD) and reconfirmed GHD may have increased metabolic risk after GH treatment withdrawal at final height (FH).

Aim: of our study is to compare growth response and metabolic profile in idiopathic COGHD adolescents with reconfirmed GHD in comparison to GHD subjects who normalized their GH response at transition phase.

Patients and Methods: twenty subjects (8 F) (age 17.0 ± 1.4 yrs) with reconfirmed GHD at retesting (peak of GH < 19 ng/ml after GHRH+Arginine), and twenty adolescents (8 F) (age 16.8 ± 1.0 yrs) with sufficient GH response to the test (GHS) were enrolled.

In all patients the following parameters were evaluated at diagnosis of GHD during childhood, and before and after 6 months of GH withdrawal at the attainment of FH: height, weight, height velocity (HV), bone age (BA), waist circumference (WC), hip circumference (HC), waist/hip ratio (WHR), waist/height ratio (WHtR), IGF-1, glucose, insulin, HOMA, QUICKI index, total-, HDL- and LDL- cholesterol, triglycerides, atherogenic index (AI), fibrinogen and homocysteine.

Results: At diagnosis during childhood, subjects with reconfirmed GHD were younger than GHS subjects (7.0 ± 4.4 vs 10.6 ± 2.9 yrs, $p < 0.02$) and had lower SDS (- 3.0 ± 1.1 vs - 2.2 ± 0.8 , $p = 0.03$), HV SDS (- 3.6 ± 1.1 vs - 2.2 ± 1.5 , $p = 0.007$), HDL-C (47.6 ± 12.6 vs 60.1 ± 15.6 mg/dl, $p < 0.03$) and higher levels of AI (3.6 ± 1.1 vs 2.6 ± 0.9 , $p < 0.02$), fibrinogen (300.7 ± 46.6 vs 266.3 ± 44.9 mg/dl, $p < 0.05$) and homocysteine (11.8 ± 3.9 vs 8.8 ± 3.4 μ mol/L, $p < 0.04$).

The groups became comparable for all these parameters during GH treatment.

At the attainment of FH the total gain in H SDS was higher in GHD in comparison to GHS young adults (2.2 ± 1.6 vs 1.2 ± 0.4 , $p < 0.03$) while all other anthropometric and metabolic parameters were comparable between the two groups.

Six months after GH withdrawal, GHD patients showed higher BMI SDS (0.30 ± 1.5 vs -0.67 ± 1.0 , $p < 0.05$), WHtR (0.50 ± 0.06 vs 0.45 ± 0.03 , $p < 0.008$), total cholesterol (157.7 ± 22.3 vs 141 ± 22.1 mg/dl, $p < 0.05$), AI (3.4 ± 0.5 vs 2.6 ± 0.7 , $p < 0.002$), fibrinogen (307 ± 45.7 vs 272.3 ± 46.1 mg/dl, $p < 0.05$) and homocysteine (12.1 ± 4.6 vs 9.2 ± 2.9 μ mol/L, $p < 0.05$) and lower levels of HDL cholesterol (47.8 ± 8.8 vs 55.8 ± 10.3 mg/dl, $p < 0.03$) than subjects with sufficient GH secretion.

Conclusions: Discontinuation of GH therapy at attainment of FH in subjects with reconfirmed GHD is associated to the development of metabolic abnormalities already 6 months after withdrawal; thus underlying the importance of an early GH restart in young adults with reconfirmed GHD.

The Influence of pituitary MRI findings on clinical presentation and growth in GH-Treated Children with Congenital Hypopituitarism

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Introduction: MRI imaging is the technique of choice in the diagnosis of children with hypopituitarism. Marked differences in MRI pituitary gland morphology suggest different etiologies of GHD, different clinical and endocrine outcome and different prognoses.

Objective: To investigate the auxological, clinical and hypothalamic pituitary-MRI features in children with non-acquired growth hormone deficiency (GHD); and determine the correlation between clinical presentation and response to treatment, and MRI findings.

Methods: Data were collected from the case notes of all patients followed for GHD in two paediatric endocrine centers in Algiers from 2008 to 2018. Patients who had undergone pituitary MRI examination were included in this study. Abnormal imaging was defined as the presence of one or more of the following three anomalies: hypoplastic anterior pituitary, truncated/absent pituitary stalk, or ectopic posterior pituitary (EPH). Patients were divided into those with normal MRI findings (group 1) and abnormal MRI (group 2).

Results: Of 355 patients followed for GHD, 242 (170 boys and 72 girls) mean \pm SD age at diagnosis 8.38 ± 4.1 [0.2-19] were eligible for study. MRI was normal in 135 (56%) patients (97 boys), and abnormal in 107 (44%) patients (73 boys), comprising 49 (20%) with EPH. Significant between-group differences were found for Caesarean and breech delivery, neonatal asphyxia, and hypoglycemia ($p < 0.005$), these being more frequent in Group 2.

Group 2 had more multiple pituitary hormone deficiency (MPHD) than Group 1 (45% vs 9%, $p < 0.007$). At presentation Group 2 differed significantly from Group 1 for: age 7.76 ± 4.3 vs 8.85 ± 3.9 years, $p < 0.04$; bone age delay: -3.16 ± 1.6 vs -2.44 ± 1.3 years $p < 0.01$; height (Ht) SD: -3.72 ± 1.2 vs -3.14 ± 1.1 SDS $p < 0.0001$; pre-treatment Ht velocity: -3.16 ± 1.7 vs -2.1 ± 1.8 SD < 0.001 ; and peak GH: 6.15 ± 6.1 vs 10.99 mUI/l $p < 0.0001$; but not for serum IGF1 SD: -2.29 ± 1.9 vs -1.99 ± 1.5 . Catch-up growth at one and two years was better for Group 2 vs Group 1 at 1.24 ± 0.9 vs 0.72 ± 0.8 SD $p < 0.001$; and 1.72 ± 1.04 vs 1.02 ± 0.94 , $p < 0.0001$. EPH was significantly associated with a risk of MPHD (60% vs 28%, $p < 0.001$), severe GHD (89% vs 46%, $p < 0.0001$) and better catch-up growth ($p < 0.005$).

Conclusion: Our data indicates that pituitary MRI findings, particularly EPH, are helpful in predicting response to GH therapy in children with non-acquired GHD. MRI examination should therefore be performed in all cases of proven GHD.

P2-162**Metabolic effects of growth hormone treatment in short prepubertal children: a double-blinded randomized clinical trial**

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Objective: Growth hormone (GH) is a central hormone for regulating linear growth during childhood and also highly involved in metabolism of lipids, carbohydrates and protein. However, few studies report on how treatment with GH during childhood influences metabolic parameters. Our aim was to investigate metabolic effects of different doses of GH in short children with GH peak levels in the low normal range.

Design: Thirty-five pre-pubertal short children (<-2.5 SDS), aged 7-10 years, with peak levels of GH between 7 and 14 µg/L during an arginine insulin tolerance test (AITT), were randomized to three different doses (10/30/100 µg/kg/d) of GH treatment for 2 years. The doses were blinded for both patients and study investigators. Auxological and metabolic investigations were performed. These included metabolites in blood and interstitial microdialysis fluid, dual-energy X-ray absorptiometry (DEXA), frequently sampled intravenous glucose tolerance test (FSIVGTT) and stable isotope examinations of rates of glucose production and lipolysis.

Results: At 24 months, the high dose group (HD) had higher fasting insulin compared with the standard dose (SD) and low dose (LD) groups (HD: 111.7 vs SD: 61.2 and LD: 46.0 pmol/L [$p=<0.001$]) and showed signs of insulin resistance (HOMA-IR, HD: 4.20 vs SD: 2.17 and LD: 1.71 (LD) [$p=<0.001$]). The FSIVGTT also demonstrated higher acute insulin response (AIR, HD: 667 vs SD: 418 and LD: 348 mUxL⁻¹ x min [$p=<0.05$]). Few other metabolic differences were found at 24 months but a decreased insulin sensitivity index (Si) could already be seen at 12 months for both SD and HD compared with the LD group (Si, HD: 5.4, SD: 6.4 vs LD: 10.1 [mU/L]⁻¹ x min⁻¹ [$p=<0.05$]).

Conclusion: Treatment with GH has a dose-dependent effect on insulin sensitivity in short prepubertal children leading to higher levels of fasting insulin and signs of insulin resistance in both HOMA indices and FSIVGTT examinations.

P2-163**Growth response in short preterm- born children small for gestational age in first year of growth hormone treatment**

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Background: Growth hormone (rGH) treatment is an approved growth promoting therapy in children born small for gestational age (SGA) without spontaneous catch-up. SGA infants may be born either full-term or premature. Prematurity is an additional risk factor for adult short stature. Premature children born SGA may potentially be affected by combination of the effects of prematurity and SGA status. There are only few reports on premature SGA children treated with rGH.

Aim: The aim of the study was to compare the growth response in the first year of rGH treatment short premature and mature children born SGA.

Patients and Methods: 60 (32 girls, 28 boys) short prepubertal children born SGA (mass and/or body birth length< -2 SDS) aged 6,4±1,8 yrs treated with rGH in dose 0,035 mg/kg/day. 23 of them were premature (P-SGA) and 37 full-term (F-SGA). Auxological data were assessed at baseline and after 1 year of rGH treatment.

Results: There was a significant difference in birth mass, length and gestation age between P-SGA and F-SGA group ($1563 \pm 478,6$ v $2329,5 \pm 300,9$ g, $42,5 \pm 5,7$ v $48,3 \pm 3,1$ cm and $35,2 \pm 2,6$ v $39,8 \pm 1,3$ weeks). There were no differences between MPH (mid-parental height) SD between both groups. At the start of rGH treatment P-SGA children were significantly younger ($5,2 \pm 1,8$ v $6,8 \pm 1,8$ yrs) and shorter ($-4,5 \pm 1,0$ v $-3,3 \pm 0,7$ SD) then F-SGA. The difference between children's height SD and MPH SD in P-SGS and F-SGA children ($-3,2 \pm 1,1$ v $-2,6 \pm 1,1$) was also significant.

After the first year of treatment P-SGA children were still shorter than F-SGA ($-2,7 \pm 0,9$ v $-2,3 \pm 0,7$ SD, $p < 0,05$), but their mean first-year height gain (ΔHt) SD was not significantly different from F-SGA group ($1,4 \pm 0,6$ v $1,1 \pm 0,5$ ΔHt SD, $p > 0,05$). 65,2% P-SGA children and 54% F-SGA children showed $\Delta Ht > 1$ SD after one year of treatment.

There were no differences in baseline Body Mass Index (BMI) SD and change in BMI SD after one year of rGH treatment between groups.

Conclusions: Premature and full-term short prepubertal SGA children experienced similar height gain in the first year of rGH treatment. P-SGA children qualified to rGH treatment were younger and are shorter than F-SGA children.

P2-164

Brain Magnetic Resonance Imaging in Children with Isolated Growth Hormone Deficiency and Idiopathic Short Stature Diagnoses

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Introduction: Diagnosis of growth hormone deficiency (GHD) and idiopathic short stature (ISS) is not straightforward. Nowadays growth hormone (GH) stimulation tests play a key role in the diagnosis but they are controversial due to the lack of normative data, poor reproducibility and poor disease concordance.

The magnetic resonance imaging (MRI) is also a tool in the study of patients with short stature. Structural alterations of the hypothalamic-pituitary region have been described on brain MRI from 20 to 44% in children affected by isolated GHD (IGHD).

Aim: To know the prevalence of hypothalamic-pituitary abnormalities in patients with short stature and GH treatment indication.

Methodology: Retrospective study of IGHD and ISS patients diagnosed in a tertiary hospital's Pediatric Endocrinology Unit from February 2013 to December 2017. It is standard of care in our unit to obtain an MRI on all patients prior to starting the GH treatment, regardless of the diagnosis.

Inclusion criteria: patients with harmonic short stature (height <-2 SD below the mean for age, sex and reference population), brain MRI with or without contrast with specific attention to the pituitary, at least one GH stimulation test and GH treatment indication.

Patients were defined as GHD if they had a peak of GH <7,4 ng/dL in response to stimulation tests (exercise, L-dopa or glucagon test).

In patients with normal or dissociated (normal and pathologic) tests, therapeutic trial with GH was indicated if height was <-2,5 SD and growth velocity <-1 SD.

Exclusion criteria: histories of cranial radiation, other hypothalamic-pituitary hormone deficiencies, previously known hypothalamic-pituitary abnormalities, chronic kidney disease and disharmonic short stature.

Results: 215 patients were included (95 girls), all the patients were diagnosed as IGHD.

One of the patients with pituitary hypoplasia also had a Type 1 Chiari anomaly.

All other findings were Type 1 Chiari anomalies.

No images of cranial tumors were found.

Total of patients and brain MRI results

	Normal pituitary region	Pituitary hypoplasia	Ectopic neurohypophysis	Pituitary cyst	Other findings*
IGHD (n:215)	163 (75,8%)	37 (17,2%)	2 (0,9%)	8 (3,7%)	5 (2,3%)

IGHD: isolated growth hormone deficiency.

*Other findings, i.e. Type 1 Chiari anomalies.

Conclusions:

- Brain MRI is helpful in the study of children with IGHD and ISS.
- The prevalence of abnormalities in the hypothalamic-pituitary region in these children is higher than in general population.
- The main IGHD-related brain pathology encountered was pituitary hypoplasia (17,2%).

P2-165

The clinical significance of post-sleep growth hormone levels in the diagnosis of growth hormone deficiency

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Background: The growth hormone (GH) stimulation test, which requires multiple blood sampling, should be performed to confirm the diagnosis of growth hormone deficiency because of the pulsatile secretion of GH. In addition to hypoglycemia, L-dopa and arginine, deep sleep is also known as an important stimulator of GH secretion.

Objectives: The aim of study was to assess the accuracy and predictive value of the test of post-sleep GH secretion in diagnosing GHD, and compare with standard GH stimulation tests.

Methods: 100 cases of GH stimulation test were analyzed. GH stimulation was assessed in two standard stimulating tests. All individuals had short stature below the 3rd percentile, and insulin-like growth factor (IGF)-1, IGF-BP3, peak GH levels at GH stimulation test, and post-sleep GH (1 hour after deep sleep) levels were measured. The difference between GH deficiency (GHD, n=63) and non-GHD (n=37) group was analyzed.

Results: The chronologic age, bone age, height standard deviation score (SDS) and IGF-1 SDS were not significant between GHD and non-GHD group. The post-sleep GH level was statistically significant (5.00 ± 3.63 ng/mL in GHD and 10.48 ± 6.72 ng/mL in non-GHD group) (*P value < 0.001*). Also, the post-sleep GH level was positively correlated with GH peak ($r=0.47$, *P value < 0.001*). Glucagon stimulation test showed the highest sensitivity (100%), specificity (100%), positive predictive value, negative predictive value among GH stimulation tests. The level of post-sleep GH above 6.95 ng/mL indicated non-GHD with 70.3 % sensitivity, 71.4 % specificity.

Conclusion: The post-sleep GH level could be used as an additive tool in the diagnosis of GHD. Glucagon was the most useful test among GH stimulation tests. Further investigation is required on the diagnostic criteria of GHD and predictors of response to GH treatment.

P2-166**Prediction of the first-year response to growth hormone treatment in prepubertal Korean children with idiopathic growth hormone deficiency: analysis of data from the LG Growth Study database**

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Background: Insufficient data exist for the prediction of the first-year response to growth hormone (GH) treatment in Korean prepubertal children with idiopathic GH deficiency (GHD).

Methods: Data from children (n = 345) who were in the LG Growth Study Database or had participated in other relevant clinical trials were used to develop a model. All included patients had been diagnosed with idiopathic GHD with maximum GH levels of less than 10 ng/mL in at least two GH stimulation tests and presented in a prepubertal state during the first year of GH treatment. Children with pituitary or hypothalamic lesions were excluded.

Results: In the first year of GH treatment, the change in height standard deviation score (SDS) was correlated positively with weight SDS ($\beta = 0.304$, $P = 0.0003$), body mass index (BMI) SDS ($\beta = 0.443$, $P < 0.0001$), paternal height ($\beta = 0.054$, $P = 0.0013$), paternal height SDS ($\beta = 0.296$, $P = 0.0013$), mid-parent height (MPH; $\beta = 0.026$, $P = 0.0268$), and MPH SDS ($\beta = 0.421$, $P = 0.0004$) but negatively with age ($\beta = -0.294$, $P < 0.0001$), bone age ($\beta = -0.249$, $P < 0.0001$), and MPH SDS minus baseline height SDS ($\beta = 0.099$, $P = < 0.0001$). A growth prediction model was established using the following variables: age, BMI SDS, bone age, paternal height, MPH SDS minus height SDS, initial dose of GH, and sex. The equation describing the predicted height SDS during the first year of GH treatment is as follows: $\Delta\text{Height SDS during 1}^{\text{st}} \text{ year of GH treatment} = 1.06 - 0.05 * \text{age} + 0.09 * (\text{MPH SDS minus baseline height SDS}) + 0.05 * \text{BMI SDS}$. This model explained 19.6% of the variability of the response with an error (SD) of 0.31. This model explained 19.6% of the variability in the response, with an error (SD) of 0.31.

Conclusions: In Korean prepubertal children with idiopathic GHD, the first-year response to GH treatment was negatively correlated with chronological age and positively correlated with BMI and the difference between their MPH SDS and a child's present height SDS.

P2-167**Adherence and long-term outcomes of therapy in pediatric subjects in Argentina using easypod™ electromechanical device for growth hormone treatment: the Phase IV multicentre Easypod™ Connect Observational Study (ECOS)**

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The Easypod™ Connect Observational Study (ECOS) assessed real-time adherence in patients from 24 countries who were receiving recombinant human growth hormone (r-hGH; Saizen®) via easypod™, which is an electronic injection device. Overall, ECOS showed mean adherence was maintained at ~80% for up to 3 years. Here, we assess the adherence to r-hGH administered via easypod™ in the Argentinian cohort of patients from ECOS (NCT01582334).

Patients aged 2–18 years treated with r-hGH administered via easypod™ for ≥6 months and ≤5 years, with a documented start date were eligible. Good adherence (proportion of days with injection received/days with injections planned) was defined as ≥80%. Growth outcomes (change in height standard deviation score [SDS] and change in height velocity SDS) and trends between adherence and growth outcomes were secondary outcomes. Adherence data were downloaded from the easypod™ device; demographic, auxological and diagnostic data were taken from medical notes. All analyses were descriptive.

Sixty-eight patients overall were included in the observational multicenter study (median age 11 years, 71% male and 29% female); 63 patients with adherence data for the 3 months after starting treatment were included in the easypod™ adherence data analysis set. The patient diagnoses were: 44 had growth hormone deficiency (GHD), 11 were small for gestational age (SGA) and eight had Turner syndrome (TS); 33 were growth hormone naïve. After 1 year of treatment, median (Q1:Q3) adherence in the easypod™ adherence data analysis set (N=49) was 88.5% (67.9%:95.6%). Good adherence decreased each year but was maintained to 3 years: 81.0% (53.2%:93.5%); N=17. After 1 year, the median (Q1:Q3) change in height SDS was 0.43 (0.21;0.64) and the change in height velocity SDS was 2.02 (0.33;4.30). Sub-analysis of adherence and growth outcomes at 1 year in patients with no missing data and no gaps in treatment >1 week (N=22) produced similar results: change in height SDS was 0.45 (0.21;0.64) and change in height velocity SDS was 2.15 (0.61;4.30). One-year growth outcomes in r-hGH treatment-naïve patients showed variable outcomes based on the origin of GHD. There was a positive trend between adherence and change in height SDS at 1 year for patients with GHD, although the number of patients was small (n=44).

In agreement with the results from the global analyses of ECOS, treatment with r-hGH administered via easypod™ led to high adherence rates in this representative population from Argentina. Overall, 1-year growth outcomes were clinically meaningful.

P2-168**Adherence and long-term outcomes of therapy in pediatric subjects in Slovakia using easypod™ electromechanical device for growth hormone treatment: the Phase IV multicentre Easypod™ Connect Observational Study (ECOS) Ľudmila Košťálová, Svetlana Bieliková, Miriam Čiljaková, Adriana Dankovčíková, Juliana Ferenczová, Slavomíra Kyšková, Eva Mendelová, Zuzana Pribilincová, Vilja Šandriková, Lubica Tichá, Marcela Balošáková**

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The global Easypod™ Connect Observational Study (ECOS) reported that adherence to recombinant human growth hormone (r-hGH; Saizen®) was maintained ~80% for up to 3 years. We now report the adherence outcomes in the cohort of ECOS patients in Slovakia (NCT01400984).

Patients aged 3–16 years treated with r-hGH administered via easypod™ from ≥4 months to 4 years and with a documented start date were included. Good adherence (proportion of days with injection received/days with injections planned) was defined as ≥80%. Secondary outcomes included change in height standard deviation score (SDS), change in height velocity SDS and trends between adherence and growth outcomes. Data on adherence were downloaded from the easypod™ device; demographic, auxological and diagnostic data were taken from medical notes. All analyses were descriptive.

Ninety-two r-hGH-naïve patients were included (median age 9 years; 39% female, 61% male; 36 had growth hormone deficiency [GHD], 48 were small for gestational age [SGA] and eight had Turner syndrome). Data from 80 patients with adherence data for ≥3 months after starting treatment were analysed. Median (Q1;Q3) treatment duration was 845 (542;1063) days and the median starting dose was 0.0318 (0.028;0.034) mg/kg. Overall median adherence was 92.35%. When analysed by 1-year intervals, median adherence was 95.5% to 1 year, 93% to 2 years and 83% to 3 years.

After 1 year, the overall change in growth outcomes was clinically meaningful: median change in height SDS was 0.49 (0.37;0.62) and median change in height velocity SDS was 2.53 (1.32;3.87). Analysis of growth outcomes at 1 year in patients who had no missing data and no gaps in treatment >1 week (complete analysis set [CAS]; N=52) produced similar results: overall median adherence was 93%, median change in height SDS 0.49 (0.37;0.62) and change in median height velocity SDS 2.54 (1.54;3.73). Up to 1 year the Spearman product-moment correlation between adherence and change in height SDS was positive and significant ($P=0.0143$) in the subset of patients with GHD.

Overall median adherence to treatment up to 3 years was >90% in this cohort of r-hGH-naïve patients. Growth outcomes were clinically meaningful and similar among all patients, and a positive association was seen between adherence and growth outcomes at 1 year for patients with GHD.

P2-169**Experience of Growth Hormone Therapy in Two Cases with Congenital Adrenal Hypoplasia**

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Introduction: DAX1 (NROB1) mutation, that is among the causes of primary adrenal insufficiency; is revealed with X-linked congenital adrenal hypoplasia and hypogonadotropic hypogonadism. Growth hormone (GH) deficiency is not common in affected individuals. In the literature, there are few cases of GH treatment. Growth hormone therapy in two cases with DAX1 gene mutation were evaluated in clinical features and treatment responses.

Case 1: A 4-year-11 months old boy, was born at 3700 g at 38th gestational week.. He was vomiting and weight loss for the first time at age of 1 month. His hormonal evaluation, ACTH (adrenocorticotrophic hormone) was very high, that was compatible with adrenal hypoplasia. In further analysis DAX-1 mutation was revealed. In spite of appropriate medical treatment, the annual elongation was 3 cm. In the examination performed at 3 years and 7 months old weight was 10.3 kg (-3.9 SD); height was 79 cm (-5.5 SD); IGF-1 was 66.2. Bone age was 1 year - 1 year and 3 months. Neurosecretory dysfunction was revealed in case that growth hormone deficiency was investigated. Height growth of case in growth hormone therapy has 7 cm per year .

Case 2: A 17-year-old male patient referred to our clinic at the age of 8 years and 7 months. He was born at 39 th gestational week at 4500 g. At the age of 2 years, he presented with vomiting and convulsion. He was diagnosed with familial glucocorticoid deficiency in other center. In the advanced examination, DAX-1 mutation was revealed. At the time of initial admission to our clinic, the patient's weight was 36.5 kg (97p>, 1.75 SD), and the height was 118 cm (3-10 p, -2.15 SD) and he was prepubertal. His height growth for the last 1 year was insufficient 3.6 cm / year despite the appropriate treatment for primary disease. Growth hormone stimulation tests were result with BH deficiency. At 10 year 10 months old he was started on GH therapy and had an average annual growth rate of 5 cm.

Conclusion: In the DAX1 mutation, that is the most common cause of congenital adrenal hypoplasia, GH deficiency is not an expected finding and is rarely reported. We shared our experience with growth hormone treatment in two cases with DAX1 mutation. Despite a relatively good growth rate was observed in the first case, the rate of elongation in both cases was lower than expected.

P2-170

Growth hormone therapy in patients with SGA short stature improves body composition by increasing muscle mass and bone mineral density rather than decreasing fat mass

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Background: Children born SGA have been implicated to be at higher risk for subsequent obesity; however, the body composition, especially fat distribution, in SGS short stature (SGA-SS) patients and the effects of growth hormone (GH) therapy on body composition in SGA-SS have not been fully studied.

Purpose: To unravel the effects of GH therapy on body fat mass, body fat distribution, muscle mass, and bone mineral density (BMD) in SGA-SS.

Method: Thirty pre-pubertal subjects with SGA-SS (14 boys and 16 girls, mean age at GH commencement 4.1 ± 1.1 years old) were included. Data on cumulative dose of GH, height (HT)-SDS, BMI-SDS, IGF-1 SDS, body composition by DXA analysis, and fat distribution by abdominal CT analysis obtained before and 1-year after GH treatment were retrospectively evaluated based on medical records. Parameters of body composition included percent fat mass (%FM) and percent muscle mass (%MM). Bone size-corrected volumetric lumbar BMD (vBMD) was calculated. Statistical analysis was performed using paired t-test or Pearson's correlation analysis. This study was approved by the institutional ethical committee.

Results: HT-SDS prior to GH treatment (Pre-HT-SDS) was -2.75 ± 0.43 SD and this was not associated with IGF-1 SDS or BMI-SDS. However, Pre-HT-SDS was positively and negatively associated with %MM($r=0.59$, $p<0.001$) and %FM($r=-0.58$, $p<0.001$), respectively. vBMD showed no association with Pre-HT-SDS. Abdominal CT revealed that amounts of visceral (VAT) and subcutaneous adipose tissue (SAT) were not elevated (VAT 4.22 cm^2 , SAT 11.36 cm^2). These findings suggest that impaired acquirement of muscle mass may be pathogenically associated with the development of SGA-SS. Upon 1-year GH treatment, HT-SDS and IGF-1 SDS increased significantly, although Δ HT-SDS was not associated with Δ IGF-1 SDS. Cumulative GH dose showed weak association with Δ HT-SDS ($r=0.38$, $p<0.05$). %FM significantly decreased by GH treatment, whereas GH treatment significantly increased %MM and vBMD. Abdominal CT showed that the amount of VAT slightly increased after GH therapy (5.32 cm^2), but the value still resided within the normal reference levels. Amount of SAT was not affected (9.36 cm^2). These results suggest that decreases in %FM by GH treatment was mainly caused by increases in muscle mass and bone mineral density.

Conclusion: GH therapy in children with SGA-SS increased HT-SDS and this was associated with improvement of body composition by increasing muscle mass and bone mineral density rather than reducing fat mass.

P2-171

Final height in GH-deficient paediatric patients: a nationwide experience

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Background: The primary goal of GH treatment in GHD children and adolescents is to normalize height, in order to attain an adult height within the target height (TH) range.

Aim: to investigate height improvement in GHD paediatric patients treated with GH in our Country.

Subjects: 737 patients with isolated GHD (39.5% females) from 13 tertiary Centres for Paediatric Endocrine Care of our Country diagnosed between 1991 and 2013. Near adult height (NAH) was recorded at GH treatment stop (growth velocity -GV- < 2 cm/year).

Inclusion Criteria: in keeping with national laws, GHD was defined as 1. height < -3 SDS OR height < -2 SDS and GV < -1 SDS OR height < -1.5 SDS than TH and GV < -2 SDS AND 2. serum GH below 10 ng/ml after two standard stimulation tests (20 ng/ml if GHRG + arginine test).

Exclusion Criteria: any condition which could affect linear growth.

Results: TH was -0.9 SDS. At start of treatment (baseline): males were older than females (10.6 vs 9.6 years, $p <0.001$); height was -2.2 SDS (vs TH $p <0.001$); mean GH dose 0.22 mg/kg/week. At puberty onset: age 11.3 and 12.5 years in females and males;

height -1.3 SDS (vs baseline p <0.001; vs TH p <0.001). At the end of treatment: age 14.8 and 16.3 years in females and males; height -0.8 SDS (vs baseline and puberty onset p <0.001; vs TH p = ns); mean GH dose 0.18 mg/kg/week (vs baseline p <0.001). NAH was significantly and positively correlated with TH, baseline height and height at puberty onset (p <0.001 for each), but not with baseline age and GH dose. The regression analysis showed that baseline height and TH were the most important factors affecting NAH.

Discussion: in our real-life nationwide study, the patients seem to be older than data from literature, but NAH is within the genetic growth potential. Most of them could have a transient prepubertal GHD (priming with sexual steroids was never performed), but a delay in referral to the tertiary Centres for Paediatric Endocrine Disease could also account for this finding. The baseline GH dose seems similar to what reported in literature and decreased during the follow-up. Patients recruitment and data collection about GH retesting, IGF1, and MRI findings are still ongoing.

P2-172

Differences of Efficiency of Treatment of Isolated Growth Hormone Deficiency and Panhypopituitarism in Children in Real Clinical Practice

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Introduction: Deficiency of growth hormone (GH) in children is manifested by pronounced stunting (below -2 sigma abnormalities (SD)). Frequency of occurrence varies from 1:4000 to 1:10000 newborns.

Objective: To assess the effectiveness of treatment by comparing the dynamics of growth of children with isolated growth hormone deficiency (IGHD) and of children with panhypopituitarism (PHP).

Materials: Medical History of 53 patients aged from 3 to 18 years diagnosed with IGHD and PHP in 1998-2018 have been analyzed in the Republican Center for Pediatric Endocrinology.

Findings: Among 53 patients participating in the study (66% girls, 34% boys) 72% is with IGHD and 28% with PHP. It was revealed that before treatment, 39 patients had a significantly short stature (from -6 to -2.01 SDS); SDS of 14 patients (2 of them with PHP) was from -1.9 to -1. At the time of diagnosis, the mean height SDS was -2.3 in children with IGHD, while after completion of treatment, SDS was -1.4; height SDS was -2.3 before and -0.7 after treatment in children with PHP. The largest values of STH maximum level according to stimulation tests was 6.8 ± 5.2 ng/ml in group with IGHD and 3.6 ± 3.3 ng/ml in group with PHP (p <0.05). At the time of diagnosis, IGF-1 was below normal range in 72% of patients, after completion of treatment it was below normal range in 43%; at the same time, the IGF-1 level in the group with PHP was lower compared to the IGHD group (p <0.05) and were observed in 71.4 % of children. After GH treatment completion, IGF-1 remained below reference values in 57.1% of patients with PHP. A lagging of the bone age from the passport in the IGHD group before treatment was 2 years 5 months \pm 1 year 3 months, after treatment it was 3 years 1 months \pm 2 years 1 month; while in the group with PHP it was 3 years 2 months \pm 2 year 8 months before

and 3 year 1 month \pm 2 year 7 months after treatment (p <0.05). The average dynamics of growth during the entire period of treatment in patients with IGHD is 6.9 ± 1.62 cm/year, while in patients with PHP it is 6.2 ± 2.73 cm/year (p <0.05).

Conclusion: Comparative analysis of the effectiveness of growth hormone treatment showed a significant dynamics of growth, more obvious in patients with IGHD.

P2-173

Implementation of a growth disorders related twinning program in pediatric endocrinology – is it necessary and feasible?

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Background: Currently, only two centers for diagnosis and treatment of growth disorders are operating in the Western and Eastern parts of Bulgaria. About 200 children are currently GH treated while at least as many children with growth disorders from mostly Central Northern and Southern Bulgaria are presumably not diagnosed. Thus inequalities in children's access to health care are created. In order to correct this and to quickly align practices between existing tertiary centers, the twinning program "Partners4Growth" was created, discussed and accepted nationally.

Results: The Program in the Pleven region, Central Northern Bulgaria (49,917 children), started in February 2018 under the active supervision from the Varna Expert Center of Rare Diseases (VECRED), University Hospital of Varna. Twinning started with e-mail communications, monthly videoconferences and exchanges between institutions. First patients' evaluation and GH stimulation tests in Pleven were done on place under the supervision from the experienced Varna team. Part of the laboratory tests were performed at VECRED initially and locally after the end of the first year. Since the start, 63 short statured children were screened, 17 (26.9%) were diagnosed with rare growth condition, and half of them (52.9%) started GH treatment with excellent initial results. For a period of 12 months, we treated a total of 9 children (55.6% male) with average age at the start of GH therapy of 9.56 ± 3.7 years and average growth velocity of 10.24 ± 4.0 cm/year.

Conclusion: The twinning enabled the quick training in initial work-up, start of GH treatment and follow up of patients of the local team. Possibilities for successful diagnosis and treatment of growth disorders on place were created within one calendar year. The next steps aim to create local multidisciplinary team expertise, acquire more experience and self-confidence while still communicating with the supervisors and thus, improve quality of care.

P2-174

Empirical change of practice in treatment of growth hormone deficient patients in order to improve 1st year height outcome

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Growth hormone (GH) has been used for the treatment of short stature due to GH deficiency (GHD) for over 60 years. Height velocity (HV) in the first year of therapy is well studied and its crucial importance for growth outcome in subsequent years is confirmed.

Objectives: The aim of this study is to assess the responsiveness to GH treatment in GHD patients of a newly established treatment center before and after change in starting GH dose.

Design: All 55 children (age range 1-18 years, 76.3% boys, a total of 3186 follow-up patient months) diagnosed with isolated or multiple non-organic GHD, treated at a tertiary University pediatric endocrinology center in the period 2011-2018, were included in the study. Patients started GH therapy at a mean age of 7.7 ± 3.7 years, and were followed up for at least one full year.

Results: With mean starting GH dose of 0.029 ± 0.007 mg/kg/d and mean GH dose for the 1st year of 0.031 ± 0.011 mg/kg/d (2011-2016), the achieved height gain for the 1st year of treatment was 8.9 ± 2.3 cm. In order to improve the 1st year growth response, new practice with higher initial GH dose was introduced since the beginning of 2017 (mean 0.030 ± 0.02 mg/kg/d). For the period 2017-2018, 71.4% patients started with GH dose >0.030 mg/kg/d, compared to 34% in the previous period (2011-2016). This lead to increased height gain (9.5 ± 1.0 cm) for the 1st year of treatment. Overall, DSDS_{height}>1.0 for the 1st year had 29.7% of all treated children in 2011-2016, while in 2017-2018 these were significantly more - 42.8% (p<0.01). No adverse effects of the treatment were seen since 2011. Initially, 36.2% of all patients showed DSDS_{height} 0.5 for the 1st year, while in 2016-2017, these decreased to 25%.

Conclusion: Our data support the evidence that the starting GH dose is important for the 1st year growth response (catch-up growth) and thus, for achieving adequate treatment results in GHD patients with no increased side effects.

Key words: growth hormone, growth response, catch-up growth

Growth and Syndromes (to Include Turner Syndrome)

P2-175

The impact of Growth hormone treatment in patients with Noonan syndrome and growth hormone deficiency

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Purpose: Noonan syndrome (NS) is a genetic disorder characterized by specific features including short stature, cardiac defect, and distinctive facial dysmorphism. Human growth hormone (GH) has been used to improve growth in children with NS but there is little information how GH treatment affects height. The aim of this study is to investigate efficacy of GH treatment in Korean children with NS compared to sex and age-matched patients with growth hormone deficiency (GHD).

Methods: Retrospective analysis of the growth during 2 years in NS children with normal GH secretion. Total 17 prepubertal children with NS (boy 10, girl 7) who received GH therapy for at least 2 years were included during 2008 and 2015. The recombinant human was administered at a dose of $50-75$ µg/kg/day for 6 days a week subcutaneously. We analyzed height and height velocity before and during GH treatment. The height and height velocity were compared with children with GH deficiency (n=32) matched for age, sex as a control group.

Results: The mean age of patients with NS was 6.34 ± 2.32 years. Mutations in the PTPN11 gene were identified in 11 subjects (64.7%). Mutations in the RAF1 (1 child, 5.8%) and SHOC2 (1 child, 5.8%) genes were also found. No mutations were found in 4 of patients (23.5%). Before starting GH, the height SDS of patients was -2.63 ± 0.72 . Height SDS increased from -2.6 ± 0.72 , to -1.92 ± 0.88 , to -1.57 ± 0.94 , respectively, at the first and second year of treatment ($P<0.001$, respectively). Growth velocity in first year was 8.6 ± 1.9 cm and 7.1 ± 1.1 cm in second years of GH treatment, respectively. The Growth velocity was 9.00 ± 1.35 (cm/yr) in first year and 6.8 ± 1.11 (cm/yr) in second year with GH treatment, respectively. There were no significant differences in growth velocity and the change of height SDS with GH treatment between NS and GHD patients.

Conclusions: GH therapy can increase linear growth in Korean prepubertal children with NS. In addition, the growth response of GH in NS patients is similar to children with GHD.

P2-176**Efficacy and safety of growth hormone (GH) in the treatment of children with hypochondroplasia (HCH): comparison with a historical cohort of untreated children with HCH**

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Hypochondroplasia (HCH) is a skeletal dysplasia, mainly caused by mutations in the fibroblast growth factor receptor3 (FGFR3) gene and characterized by disproportionate short stature.

Our main was to determine the efficacy of growth hormone therapy in children with HCH, compared with a historical cohort of 40 untreated children with HCH.

Diagnosis of subjects was confirmed by the Bone Dysplasia Center². Height standard deviation scores (SDS) were calculated from historical cohort-growth charts. Nineteen patients with initial height ≤ -2 SDS were treated with Saizen® (r-hGH, Merck France) with an initial dose of 0.05 mg/kg/day (dose adjusted with IGF-I levels). We analyzed only 8 patients (4 males) treated during at least 5 years, at a mean age of 6.8 (± 2.6) yrs.

The height gain was $+0.89 (\pm 0.60)$ SDS compared with French standard population (Sempé), but it was $+1.57 (\pm 0.8)$ SDS with the historical cohort. Correlation in height gain was observed ($p=0.04$) between the first and fifth year. Difference in height gain between 5 patients with FGFR3 mutation (1.2 ± 0.8 SDS) and the 3 patients without (2.1 ± 0.6 SDS) was not significant ($p=0.12$). Seven patients reached near final height SDS: -1.67 ± 0.8 vs Sempé but $+2.05 \pm 1.1$ vs the historical HCH cohort. No treatment related serious adverse-events were reported.

Conclusion: GH is effective in improving growth in some patients with HCH. Response during the first year is predictive of final response ($r=0.78$, $p<0.05$) and could be used to decide to continue treatment until final height.

Results	Baseline	1 st yr	2nd yr	3rd yr	5rd yr	Total gain
Height velocity (cm/yr)		8.6 ± 1.3	6.8 ± 1.5	5.3 ± 1.3	4.4 ± 1.7	
Height (SDS)/Sempé ¹	-2.44 ± 0.7	$-1.91 \pm 0.7^{**}$	$-1.47 \pm 0.8^*$	$-1.42 \pm 0.9^*$	-1.55 ± 0.8	$0.89 \pm 0.6^*$
BMI (SDS)/Sempé ¹	1.24 ± 1.2	1.11 ± 1.0	1.28 ± 1.2	1.52 ± 1.0	1.00 ± 1.1	-0.2 ± 1.4
Height / HCP ² (SDS)	0.53 ± 0.9	$1.32 \pm 0.8^*$	$1.91 \pm 1.1^*$	$2.12 \pm 1.3^*$	2.10 ± 1.1	$1.57 \pm 0.8^*$
Upper segment (SDS)	-0.44 ± 1.3	$0.12 \pm 1.1^*$	$0.46 \pm 1.3^*$	$0.91 \pm 1.4^*$	0.99 ± 0.9	$1.43 \pm 1.2^*$
% Total fat mass (SDS)	1.33 ± 0.9	$0.30 \pm 0.4^*$	$0.22 \pm 0.8^*$	$0.18 \pm 1.0^*$	$0.52 \pm 1.1^*$	$-0.81 \pm 0.8^*$

* $p<0.01$

¹vs Sempé; ²vs values of a non-treated historical cohort HCH

P2-177**Five Novel Variants of KMT2D/KDM6A Found in Seven Chinese Patients with Kabuki syndrome and a literature review of 39 patients reported in China**

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Objective: Report 5 new variants of 7 *KMT2D/KDM6A* and summarize the clinical manifestations and the mutational spectrum of Kabuki syndrome (KS) by analyzing the reported Chinese cases.

Methods: Blood samples were collected for whole-exome sequencing (WES) for 7 patients and their parents if available. Phenotypic and genotypic spectra of 39 previously published unrelated Chinese KS patients were summarized.

Result: Genetic sequencing identified six variants (c.3926delC, c.5845delC, c.6595delT, c.12630delG, c.16294C>T, and c.16442delG) in *KMT2D* gene and one variant (c.2668-2671del) in *KDM6A* gene. Of them, 4 variants (c.3926delC, c.5845delC, c.12630delG, and c.16442delG) in *KMT2D* gene and the variant (c.2668-2671del) in *KDM6A* gene were novel. Combining with previously published Chinese KS cases, the patients presented with five cardinal manifestations including facial dysmorphism, intellectual disability, growth retardation, fingertip pads and skeletal abnormalities. In addition, 25% (4/16) patients showed brain abnormalities, such as cerebellar vermis dysplasia, thin pituitary and white matter myelination delay, corpus callosum hypoplasia and Dandy-Walker malformation.

Conclusion: We reported five novel variants in *KMT2D/KDM6A* genes. A subset of Chinese KS patients presented with brain abnormalities that were not previously reported. Our study expanded the mutational and phenotypic spectra of KS.

Adult height of patients enrolled in PATRO Children, an ongoing observational study of the long-term safety and effectiveness of Omnitrope®

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Objectives: PATRO Children is an observational, international, longitudinal study of the long-term safety of a recombinant human growth hormone (rhGH; Omnitrope®, Sandoz). The effect of rhGH treatment on growth and adult height (AH) is assessed as a secondary objective of the study.

Methods: This ongoing study is conducted in hospitals and specialised endocrinology clinics across 14 countries. The study population includes infants, children and adolescents receiving Omnitrope® therapy according to country-specific prescribing information. Height velocity (HV, cm/year), height standard deviation score (HSDS), and HVSDS are derived from height measurements and country-specific reference tables. It is anticipated that patients will be treated with Omnitrope® for growth promotion in the study until they achieve AH. Patients are considered to have reached AH if they discontinue the study due to reaching AH/bone age maturity, or reaching near AH.

Results: As of January 2019 (over 13 years), 5777 patients were enrolled and included in the effectiveness population. Overall, 85.0% of patients were rhGH naïve at study entry and 14.9% had previously received other rhGH treatment. To date, 1209 (20.9%) patients (male, n=626; female, n=583) have reached AH, of which 925 (76.5%) patients were rhGH naïve and 283 (23.4%) were not. Of the patients who reached AH, 772 (63.9%) had growth hormone deficiency (GHD), and 309 (25.6%) were born small for gestational age (SGA). Among GHD patients who reached AH, 479 (62.0%) were male and 293 (38.0%) were female; mean (SD) baseline HSDS was -2.12 (1.02); at AH, mean (SD) HSDS was -1.28 (1.09). The mean (SD) difference in AH and target height was -4.55 (7.20) cm, and the mean (SD) difference between AH SDS and target height SDS was -0.87 (1.05). In SGA patients who reached AH, 123 (39.8%) were male and 186 (60.2%) were female. Mean (SD) baseline HSDS was -2.26 (1.11); at AH, mean (SD) HSDS was -2.07 (1.20). The mean (SD) difference in AH and target height was -6.82 (6.97) cm, and the mean (SD) difference between AH SDS and target height SDS was -1.40 (1.08).

Conclusion: Based on this analysis, Omnitrope® treatment improves AH of children with GHD and SGA children in real-life clinical practice. The PATRO Children study is ongoing and will continue to provide further long-term information on AH in children receiving Omnitrope® in these and other approved indications.

Unusual Case of Patient with Klinefelter Syndrome With Shox Deletion Born to the Mother With Leri-Weill Dyschondrosteosis

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Introduction: Klinefelter syndrome (KS) describes the phenotype of the most common sex chromosome abnormality in humans. About 80% of KS patients have 47,XXY karyotype, while rest of the patients can have mosaicism or other numeric or structural sex chromosome abnormalities. Tall stature is one of the hallmarks of KS and it is thought to be due to supernumerary X chromosome leading to SHOX gene overdosage. Deletion of SHOX gene, on the contrary, has been related to impaired growth in patients with Leri-Weill dyschondrosteosis (LWD), Langer mesomelic dysplasia and Turner syndrome, but also in some cases of idiopathic short stature.

Case Report: The proband is 14.6 year old boy evaluated for obesity (height 170.6 cm, + 0.4 SDS, weight 91.5 kg, +2.41 SDS, BMI 31.4 kg/m², + 2.19 SDS). At examination he had penis buried in fat tissue, with testes size Prader 4-5, pubic hair Tanner 3 and adipomastia with enlarged areolas. His laboratory finding revealed elevated gonadotropins (LH 11.9 IU/L, ref. 0.2-5; FSH 25.5 IU/L, ref. 1.2-5.8; testosterone 7.9 nmol/l, ref. 3-27) and subsequently KS was suspected. The karyotyping revealed 46,XXY/46,XY mosaicism with one derived X chromosome and 3.5% 46,XY cells (mos 47,X,der(X)del(Xp)dup(Xq)(Xq28-Xq27.2::Xp22.32-Xq28), Y/ 46,XY). Further cytogenetic analysis with FISH proved deletion of pseudoautosomal region 1 of X chromosome including SHOX gene.

Proband was in custody of his grandmother (on father's side), so his parents were invited for further genetic evaluation. His father has 46,XY, normal male karyotype and normal phenotype. His mother is disproportionately short (height 155 cm, -1.3 SDS, arm span 152 cm) and has phenotypic features of LWD (mesomelic limb shortening, Madelung deformity). Her karyotyping revealed complex rearrangement of one X chromosome with duplicated Xq27.2-qter, deleted Xp22.32 region and subsequent one SHOX deletion (46,X,der(X)del(Xp)dup(Xq)(Xq28-Xq27.2::Xp22.32-Xq28).

Conclusion: To the best of our knowledge this is the first report of the patient with KS born to the mother with LWD. Although tall stature would be expected, SHOX gene deletion might have contributed to normal stature of our patient. In KS patients carrying complex chromosomal rearrangements, detailed cytogenetic evaluation is indicated in patient and his parents. This might explain spectrum of phenotypes in patient, detect unrecognized disease in parents and provide correct genetic counseling regarding possibility of transmitting monogenic disorders in further parental pregnancies or in case of option for proband's fertility preservation.

P2-180**Sudden death in an infant attributed to arrhythmia associated with Beckwith-Wiedemann Syndrome due to hypomethylation of imprinting control region 2 on chromosome 11p15.5**

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Introduction: Hypomethylation at the imprinting control region 2 (IC2) on chromosome 11p15.5 is the commonest identifiable cause of Beckwith-Wiedemann Syndrome (BWS). IC2 is located in *KCNQ1* intron 10 and is associated with Long QT syndrome (LQTS). A recent consensus statement on BWS¹ recommends annual cardiac evaluation with electrocardiogram (ECG) in these patients. The natural history of LQTS secondary to hypomethylation at IC2 in BWS is unknown, despite it being the commonest aetiology. It is also unknown whether adequate attention is paid to the risk of arrhythmias in patients with IC2 lesions by multidisciplinary teams managing patients with this condition. Sudden death due to ion channel disease is made on the strength of negative autopsy with ECG, personal or family history or molecular diagnosis of ion channel pathology². We report a case of infant death attributed to arrhythmia associated with BWS.

Case Report: A female neonate from in-vitro fertilisation, born to a primigravida mother with benign intracranial hypertension, presented with hypoglycaemia on day four of life. Congenital hyperinsulinism was confirmed and responded to diazoxide (10mg/kg/day) and chlorothiazide (6.5mg/kg/day). She had gastroesophageal reflux disease, which responded to ranitidine. A swallow assessment showed safe swallow. Cardiac assessment was normal. She tolerated a six hour fast prior to discharge and following this, blood glucose control was excellent. Genetic tests confirmed BWS with hypomethylation at KCNQ1OT1: TSS-DMR located within 11p15.5.

At four months of life, the mother was playing with the child in her arms when she suddenly became floppy and blue. Resuscitation failed and she was pronounced dead. Hypoglycemia was excluded and an autopsy, including toxicology, found no cause of death. There was no milk in the tracheo-bronchial tree and no histological abnormalities in the lungs or oesophagus. The pancreas showed the histology of diffuse hyperinsulinism. Cause of death was considered to be due to arrhythmia.

Conclusion: This is to our knowledge, the first report of an infant death attributed to arrhythmia associated with BWS. Prospective studies are required to examine the natural history of cardiac arrhythmia in BWS patients with IC2 abnormalities. Given the location of IC2 in the *KCNQ1* gene it is possible that mutations, both genetic and epigenetic, may give rise to both BWS and LQTS.

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P2-181**A novel case of paternal isodisomy for chromosome 7 associated with overgrowth**

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We report a pediatric patient with an undiagnosed and complex medical manifestation who was shown to have paternal isodisomy at chromosome 7. Our case is a female patient presented for increasing overweight, parotid hemangioma and gastroesophageal reflux with laryngomalacia. She was born at 35+4 weeks of gestation and her birth weight, length and occipitofrontal circumference (OFC) were 2500 g, 49 cm and 33 cm, respectively. At the time of our visit she was 16 months old, her weight was 16.9 kg and her BMI 23.95. In order to detect the molecular basis of this extreme weight gain, we decided to perform whole-exome sequencing (WES) on genomic DNA isolated from peripheral blood leucocytes of the proband and her parents: WES data analysis resulted normal, with no detection of any sequence variants clearly associated with overgrowth phenotypes.. The analysis using SNP-CGH probes suggested that the genome of the patient had a loss of heterozygosity without any CNVs in chromosome 7, which implied that she had paternal isodisomy of the entire of chromosome 7 (IsoD7pat). IsoD7pat is extremely rare, and only four cases have been previously reported. As these cases were accompanied by autosomal-recessive disorders which are likely to be involved in growth restriction, the relevance of IsoD7pat to the overgrowth phenotype remains unclear. Maternal uniparental disomy for chromosome 7 is known to result in Silver-Russel syndrome, characterized by intrauterine growth retardation accompanied by postnatal growth deficiency, but little is known about IsoD7pat, which is extremely rare. Up to now, the other four reported patients did not express overweight, probably due to their autosomal recessive underlying condition (cystic fibrosis, primary ciliary dyskinesia, congenital chloride diarrhoea), to be involved in their growth restriction. We here report the second case of the IsoD7pat, without autosomal-recessive disorders, expressing a clear overweight, supporting the involvement of this imprinting disorder in determinism of overgrowth phenotypes.

P2-182**Auditory phenotypes and dynamics of hearing thresholds in 246 Turner syndrome females**

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Objectives: To describe the auditory phenotype and dynamics of hearing thresholds in patients with Turner Syndrome (TS).

Patients and Methods: Cross-section study evaluating the hearing thresholds in 246 TS patients (age range 4-44 yrs). Patients were divided into three age groups: Group 1 (79 TS, age range 4.0-12.9 yrs); Group 2 (109 TS, age range 13.0-25.9 yrs,) and Group 3 (66 TS, age range 26.0-44.9 yrs.). Pure tone audiometry (PTA) with evaluation of frequencies ranging from 250 to 12,000 Hz was assessed to define 5 types of audiograms according to HEAR classification: 1. Increasing (hearing loss at low frequencies); 2. U-shaped or Dip (medium frequency hearing loss HL); 3. "Gentle" slope (hearing loss at high frequencies); 4. "steep" slope (hearing loss at high frequencies); 5. Plate.

Results: 198 (56.1%) TS females presented hearing loss (HL). Percentage of TS HL patients increased with age (Group 1 31.6%, Group 2 37.6%, Group 3 68.2%; p < 0.001). Only in Group 3, ENT remote pathology was more frequently positive in TS with HL (80% vs 42.9%, p = 0.003). 80.6% of TS had a slight degree of HL without any significantly difference among the 3 groups (Group 1 92.0%, Group 2 81.6%, Group 3 73.3%; p = n.s.); 32.4% had sensorineural HL (SNHL) that significantly increased with age (Group 1 12.0%, Group 2 71.1%, Group 3 95.6%; p < 0.001). On the contrary, the prevalence of conductive HL (CHL) significantly decreased with age (Group 1 88.0%, Group 2 28.9%, Group 3 4.4%; p < 0.001). Type 5 was the more frequent audiogram documented (34.2%), followed by types 2 (28.7%) and 3 (18.5%). Types 1 (6.5%) and 4 (12%) were rarer. Only the frequency of type 5 audiogram significantly decreased with age (Group 1 60.0%, Group 2 31.6%; Group 3 22.2%; p < 0.001).

The univariate and multivariate logistic regression analyses demonstrated that age (Odds 1.62) and a positive ENT remote pathology (Odds 2.007) were significant predictors of deterioration of auditory outcome in TS.

Conclusions: ENT remote pathology and age are predictive factors for HL in TS. SNHL in TS dramatically increased from the age of 13 yrs. Type 5 is the more frequent audiogram in TS under the age of 45.

P2-183**The Prevalence of Celiac Disease (CD) in Children with Type 1 Diabetes Mellitus (T1D); Does CD adversely affect linear growth in these children?**

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The prevalence of biopsy-proven CD in T1D in pediatric populations widely ranges between 2.6 in Finland to 16.4 in Algeria. Many patients with CD and T1D are either asymptomatic (silent CD) or present with only mild symptoms. CD children may be less likely to show overt growth failure but can have weight and height measures at a lower growth percentile and complain of nonspecific symptoms, including anorexia and lassitude.

Aim; Patients and Methods: This cross-sectional study measured the prevalence of positive serology test and biopsy-proven CD in a large cohort of children T1D (n = 365) and compared their growth parameters on the first diagnosis with the growth of children with T1D without CD.

Table 1. Prevalence of CD in T1DM according to diagnostic criteria

Celiac Diagnostic criteria	Positive Result	Prevalence
Total TTG positive	28/365	7.67 %
ATT IgA	18/365	5%
ATT IgG	16/365	4.38%
Both ATT IgA and IgG	11/365	3%
Biopsy proved	11/28 (39%)	3 %

Table 2. Anthropometry for T1D, versus T1DM +CD. (* P < 0.05)

Groups	T1DM +CD N = 17	T1D N = 50
Age (yr)	7.99 +/- 3.5	9.1 +/- 4.2
BMISD (mean +/- SD)	-0.077 +/- 1.72	0.089 +/- 1.39
BMISD > 2 SD	2/17 = 11.76 %	6/50 = 12 %
BMISD (-1.5 to 1.5)	12/17 = 70 %	37/50 = 75 %
BMISDS (-1.5 - 2)	2/17 = 11.76 %	4/50 = 8 %
BMISDS < -2	2/17 = 11.76 %	2/50 = 4 %
HSDS (mean +/- SD)	0.33 +/- 1.40	0.27 +/- 1.29
HSDS = or > 2	0/17 = 0 %	5/50 = 10 %*
HSDS (-2 to +2)	14/17 = 82 %	44/50 = 88 %
HSDS < -2	3/17 = 17.64 %*	1/50 = 2 %

Results: The children with obesity who has celiac were short with HSDS < -2 (nutritional dwarfism) while the non-celiac group has a normal height for age.

Conclusion: The prevalence of biopsy-proven CD in our cohort was 3 %. Their BMISDS and HtSDS did not differ compared to controls with T1DM. However, children with T1D + CD had higher % of short stature compared to T1D.

P2-184**Effect of Gonadotropin-Releasing Hormone Agonists on Auxological Outcomes of Korean Boys with Central Precocious puberty and Early Puberty**

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Objective: To determine the effect of gonadotropin-releasing hormone agonist (GnRHa) treatment on auxological outcome of Korean boys with central precocious puberty (CPP) and early puberty (EP).

Methods: This study included 11 boys with CPP and 8 boys with EP who were treated with GnRHa for at least 2 years at the Pediatric Endocrine Unit of Ajou University Hospital from March 2003 to December 2015. All nineteen boys attained final adult height (FAH). Anthropometry, bone age, sexual maturity rating, and predicted adult height (PAH) were assessed every 6 months. We compared their FAH with their initial predicted adult height (PAH). Moreover, we performed a multivariate analysis of the factors associated with FAH.

Results: Mean chronological age (CA) and bone age (BA) of patients in CPP at the start of treatment were 9.32 ± 0.78 years and 12.41 ± 1.02 years, respectively. Mean duration of treatment was 2.7 ± 0.6 years. Their PAH at the start of treatment was 166.7 cm (-1.18 ± 1.33 , PAH standard deviation score [SDS]). The mean FAH in boys with CPP was 172.05 ± 6.49 cm and their FAH was significantly increased compared to their pretreatment PAH ($p = 0.043$). Mean CA and mean BA of patients in EP at the start of treatment were 10.98 ± 0.47 years and 13.0 ± 0.59 years, respectively. Their PAH at the start of treatment was 170.46 ± 4.85 cm (-0.51 ± 0.87 , PAH SDS) in EP. The mean FAH in boys with EP was 171.9 ± 4.63 cm and there was no significant difference between initial PAH and FAH in EP. The FAH was only significantly correlated with initial height before treatment.

Conclusion: The FAH was significantly higher than the initial PAH in boys with CPP who were treated with GnRHa.

P2-185**Premature infants born small to gestational age: growth dynamics in the first 5 years of life**

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Prematurity combined with intrauterine growth retardation (small to gestational age, SGA) is a potential risk factor for adverse growth prognosis. There is insufficient evidence on this issue.

Aim: to study the growth rates in preterm infants born small to gestational age, different gestational age in the first 5 years of life. Material and methods. The prospective study included preterm infants with SGA (group 1, n=100) and preterm infants corresponding to gestational age (group 2, n=69) with a division by gestational age (32-36 weeks and 22-31 weeks). Monitoring of

body length/height was carried out at birth, at 6 months, then annually. At the age of 5 years, 48 children of group 1 and 33 children of group 2 completed the study. The data are presented in the form of a median and interquartile interval with an assessment of the significance of the Mann-Whitney differences. The calculation of SD growth was carried out using the program Anthro (WHO).

Results: Body length at birth in preterm infants with gestational age 32-36 weeks corresponded to 44.0 [43.0; 45.0] cm in group 1 and 46.0 [42.0; 48.0] cm in group 2 ($p < 0.05$), significantly differing in SD relative to gestational age: -1.0 [-1.5; -0.4] SD and +0.1 [-0.7; +0.6] SD. Subsequently, children of group 1 achieved growth rates of children of group 2 by 4 years: 100.0 [94.5; 102.8] cm and 100.0 [95.7; 105.5] cm, respectively. However, only in group 1 part of children had growth rates less than -2.0 SD (24.2% - in 4 years, 24.2% - in 5 years).

Body length at birth in preterm infants with gestational age of 22-31 weeks corresponded to 34.0 [31.0; 36.0] cm in group 1 and 36.0 [33.0; 40.5] cm in group 2 ($p < 0.05$), significantly differing in SD relative to gestational age: -1.0 [-1.7; -0.4] SD and +0.5 [-0.1; +1.9] SD. During the entire follow-up period, group 1 children had significantly ($p < 0.05$) lower growth rates compared to group 2. At the age of 4 years, their growth corresponded to 94.3 [93.0; 99.0] cm, -2.0 [-2.3; -0.9] SD; in 5 years - 103.0 [99.3; 111.0] cm, -1.4 [-2.1; -0.3] SD. Growth of less than -2.0 SD was registered only in group 1 (53.3% - in 4 years, 33.3% - in 5 years).

Summary: Premature infants with SGA and gestational age of 22-31 weeks have an unfavorable growth prognosis in the first 5 years of life, which determines the direction of further research.

P2-186**Clinical features in a patient with Turner syndrome and pericentric inversion of chromosome 9**

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Turner syndrome (TS) patients are at risk for a constellation of neurocognitive and psychosocial diseases. TS is associated with an increased risk for difficulties with visual-spatial reasoning, visual-spatial memory, attention, executive functioning, motor, and math skills. Additionally, increased rates of social difficulties, anxiety, and depression are observed.

Here we report the case of a 16-years-old Caucasian girl who came to our attention at the age of 18 months due to short stature and clinical signs typical of TS. Genetic testing showed a single X chromosome and a pericentric inversion of chromosome 9 [45,X,inv(9) karyotype]. Imaging revealed no cardiovascular malformations and/or renal abnormalities. To date no autoimmune diseases have been detected.

At the time of diagnosis she presented a mild mental retardation. During the follow-up her parents did not attend educational programs prescribed by the neuropsychiatry specialist, and the patient developed a severe emotional disturbance with anxiety and a behaviour pattern characterized by complete language impairment. This behavioural phenotype was consistent with a diagnosis of autism spectrum disorder.

Inv(9)(p11q13) is the most commonly observed structurally balanced rearrangement of chromosome involving the heterochromatic region. The estimated frequency varies from 1 to 4%. Although it is widely debatable, most cytogeneticists believe that this variant is a chromosomal polymorphism of the normal human karyotype without any clinical significance. Contradictorily, many clinical investigators have suggested several associations of inv(9) with clinical diagnoses, particularly with idiopathic reproductive failure, schizophrenia, and behavioural and neurodevelopmental disorders.

The association of this rearrangement in our patient could explain the severe neurodevelopmental disorder. On the basis of our observation we stress the importance to evaluate eventual associated chromosomal abnormalities in TS patients in order to predict certain phenotypic features of these individuals. As in our patient, the presence of pericentric inversion of chromosome 9 could increase the risk of developing neuropsychiatric disorders. According to the most recent literature, we think that the early identification of psychosocial disease may facilitate the improvement of social deficits through the prompt application of appropriate educational strategies and therapeutic programs.

P2-187

"Transition Readiness in girls and young women with Turner syndrome – are they less ready?" Associations between transition readiness and diagnosis

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Objective: Young women with Turner syndrome are known to be especially at risk for lost of follow-up. Recent literature indicates that there are disparities regarding transition readiness between different chronic conditions. To assess differences in transition readiness might be crucial for identifying special needs in specific patient cohorts when preparing for transfer to adult care. Our hypothesis was, that young women with Turner syndrome would score lower than patients without a disorder-specific neurocognitive phenotype, like girls and young women diagnosed either with type 1 diabetes or with juvenile idiopathic.

Method: Patients (n=54, 27 patients with TS, 27 controls) aged 14 to 23 were recruited in a multicenter study involving 3 specialized pediatric Endocrine outpatient clinics.

We applied the recently cross-culturally adapted German version of the Transition Readiness Assessment Questionnaire (in publication, under review) to assess transition readiness in girls and young women with Turner syndrome (N=27, group TS) compared to age-matched controls.

Demographic characteristics (age, sex, first language, patient's education) were included. We gathered data on frequency of help

needed to answer the questionnaire, time needed to complete the questionnaire, and duration of the individual interview. We used descriptive statistics and conducted non-parametric Wilcoxon signed-rank test.

Results: Significant differences for transition readiness scores were found between the two study groups. Subscale 1 "autonomy" of the Transition Readiness Assessment Questionnaire showed lower scores for patients with Turner syndrome. No significant difference could be found for subscale 2 "Health Literacy" and for subscale 3 "adherence". On a single item level, two items from subscale 1 regarding appointment arrangements and one item from subscale 2 concerning knowledge about health insurance showed significant lower scores for girls with Turner syndrome. Patients with Turner syndrome needed significantly more help and more time to fill in and complete the questionnaire. Significantly longer duration of consultations for patients with Turner syndrome was recorded.

Conclusion: Lower scores for patients with Turner syndrome compared to a control group comprising patients with type 1 diabetes and juvenile idiopathic arthritis. Thus, special attention should be given to young women with Turner syndrome in the preparation for the transitional phase. By incorporating the assessment of transition readiness within the clinical setting, specialists will find it easier to identify underdeveloped skills and knowledge gaps in their patients. As patients with Turner syndrome needed significantly more time in completing the survey, sufficient time for consultation should be scheduled.

P2-188

Clinical and molecular genetic characterizations of five patients harboring mutations in the GNAS gene: a case series and literature review

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Objective: Inactivating mutations in the gene encoding the alpha-subunit of Gs (GNAS) gene, which consists of exons 1-13 and encodes the alpha-subunit of the stimulatory G protein (Gsa), are associated with several clinical syndromes, including pseudohypoparathyroidism (PHP), pseudopseudohypoparathyroidism (PPHP), and progressive osseous heteroplasia (POH).

Method: We documented patient clinical characteristics and performed targeted next-generation sequencing and Sanger sequencing. The standards and guidelines of the American College of Medical Genetics and Genomics were used to classify and interpret the pathogenicity of each genetic mutation detected.

Results: The current study presents 5 patients with different mutations within exons 1-13 of the GNAS gene and distinct clinical phenotypes (3 PHP1a, 1 PPHP, and 1 POH). These 5 patients harbored pathogenic mutations, including an intronic mutation (c.212+3_212+6delAACT), two missense mutations (c.314C>T and c.308T>C), and a deletion (c.565_568delGACT), which included one missense (c.314C>T) and one splicing (c.721+2 G>A) mutation which were never reported previously.

Conclusions: This study conducted a phenotypic and molecular assessment of patients, with diagnoses of PHP, PPHP, or POH. PHP can be difficult to diagnose because its clinical phenotype is highly variable and Gsα activity is not routinely assessed or available. Therefore, sequence of the GNAS gene serve as a method of confirming the diagnosis of PHP. In addition, it is necessary for clinicians to distinguish heterotopic ossification in POH from the AHO phenotype.

P2-189**Anophthalmia, micrognathia, combined pituitary hormone deficiency, severe growth retardation and liver dysfunction induced levothyroxine sodium powder in a boy with microdeletion of 14q22q23**

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Background: Microdeletion of 14q22q23 results in a rare chromosomal disorder associated with microphthalmia/anophthalmia, pituitary anomalies, polydactyly/syndactyly, micrognathia, growth restriction and mental retardation. Haploinsufficiency of the genes OTX2 (orthodenticle homeobox 2) and BMP4 (bone morphogenetic protein 4) are responsible for most of the phenotypic features in the 14q22q23 microdeletion syndrome. There are only a few reports about liver dysfunction induced by levothyroxine in childhood.

Case Presentation: The patient was born at 38 weeks and 5 days. His birth length and weight were 41.5cm (-3.5SD) and 1946g (-2.5SD). He showed bilateral anophthalmia, micrognathia, low set ears, micropenis, cryptorchidism at birth. He also had respiratory failure, hypoglycemia and bilateral hearing loss. The brain magnetic resonance imaging revealed anterior pituitary hypoplasia, ectopic posterior pituitary, bilateral anophthalmia and severe micrognathia. Endocrine examination revealed combined pituitary hormone deficiency. GH level was 1.2 ng/ml after arginine stimulation and IGF-1 level was low (11 ng/ml). His cortisol (1.0µg/dl) and FT4 (0.74 ng/dl) levels were low. LH, FSH and testosterone were undetectable. His karyotype was 46,XY. Array CGH revealed 7.6Mb microdeletion of 14q22.1q23.1 including OTX2 and BMP4 genes. Levothyroxine sodium powder and hydrocortisone administration started at 1 month and GH therapy started at 4 months. After starting levothyroxine sodium powder administration, he showed liver dysfunction. The levels of AST and ALT increased gradually and reached 1547 U/l and 688U/l at 3 months old. Liver dysfunction was reversed with discontinuation of levothyroxine sodium powder administration. The drug-induced lymphocyte stimulation test (DLST) using levothyroxine was positive. Instead of it, we started liothyronine at 4 months. It is difficult to control thyroid function using liothyronine because there are not appropriate markers. We changed to powdered levothyroxine tablet at 7 months. He did not show liver dysfunction under administration of these. After starting GH therapy, his growth rate improved a little. He also needed tracheotomy and gastrostomy because he could not extubate and showed difficulty in swallowing because of severe micrognathia.

Conclusion: GH therapy slightly improved growth rate in this case, but since GH deficiency was probably not only factor responsible for growth retardation, in patients with 14q22q23 deletion, GH therapy was not completely effective in stimulating normal growth. This finding is not unexpected because previous reports showed there were patients with growth retardation in the absence of GH deficiency and growth was difficult to correct with GH therapy in patients with GH deficiency.

P2-190**Growth Hormone Therapy in patients with Noonan Syndrome**

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Introduction: Noonan Syndrome (NS) is an autosomal dominant condition that affects 1 in 1000 to 2500 live births and is associated with short stature. Studies have shown that height velocity (HV) improved significantly with the use of growth hormone (GH) in the first year of treatment and sustained for the second year. We aimed to look at the effects of GH therapy in our cohort of patients with NS.

Method: In this retrospective study, we collected data on patients with NS who were treated with GH in a tertiary endocrine centre.

Results: A total of twelve patients with a mean birth weight of 3.3 kg (-0.5SDS) were included in the study (Male: 10). GH was commenced at an average age of 8 years (\pm 3.3 years) and the mean treatment duration was 3 years (range 1-8 years). The average height SDS prior to starting treatment was -2.96, which improved to -2.05 after treatment for a variable period of time, demonstrating an overall average improvement of +0.91SDS. The height SDS improved from -2.96 to -2.50 after one year of treatment and subsequently to -2.22 following two years of treatment. The mean HV prior to treatment was 5.16cm/yr and improved to 7.76cm/yr ($p=0.007$) and 6.51cm/yr ($p=0.2$) after one and two years of GH therapy, respectively. The HV dropped after three years (4.95cm/yr) but became varied over the treatment course (range 3.7 to 7.5cm/yr). The average starting dose of GH was 34mcg/kg/day, with an average maximum dose of 37mcg/kg/day during the course of GH treatment. 67% of patients had associated cardiac co-morbidities [including pulmonary valve stenosis, atrial septal defect and hypertrophic cardiomyopathy] as part of NS. Other co-morbidities included hearing problems, scoliosis, nystagmus and strabismus.

Conclusion: GH treatment in patients with NS does improve the HV in the first few years of treatment but the long term benefits remain to be ascertained.

P2-191

The first case of genetically diagnosed Cantú syndrome in China with mutation in ABCC9

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Background: Cantú' syndrome is rare disease characterized by congenital hypertrichosis, neonatal macrosomia, cardiomegaly and several other abnormalities. Gain-of-function mutations in either *KCNJ8* or *ABCC9* have been identified as the causative gene for Cantú' syndrome. Here we report the first genetically diagnosed Cantú' syndrome case in China and describe the full clinical features of the case.

Case: A 4-month-old Chinese female infant was transferred from a local hospital to our pediatric intensive care unit because of severe pneumonia and congenital heart disease without family history. She was born at 39^{+2} weeks' gestation and her birth weight was 4.6kg indicating neonatal macrosomia. A coarse face was noticed. She has flat broad nasal bridge, long philtrum (18mm) and thick lower lip vermillion. Thick scalp hair that extends onto the forehead and grows down onto the cheeks in front of the ears were observed. Her body hair, especially on the back and arms, increases. She has abundant eyebrows and curly eyelashes. Evaluations for physical growth showed body weight 6.8kg; recumbent length 66.0cm; crown-rump length 41.0cm; head circumference 41.5cm; chest circumference 43.0cm and arm span 67.0cm. Hypotonia was revealed through physical examination of nervous system. Echocardiography after hospitalization showed patent ductus arteriosus, patent foramen ovale, hypertrophied muscle bundles in the anterior wall of the right ventricle, moderate pulmonary hypertension, and left atrium and ventricular enlargement. Radiological Findings of the whole body only showed varus knee deformity. A hereditary disease was highly suspected. Then, exome sequencing was performed and a de novo heterozygote mutation in *ABCC9* gene (*c.3460C>T, p.R1154W*) was detected. Thus, an autosomal dominant Cantú' syndrome was diagnosed. Surgical closure of the PDA was performed for this infant.

Conclusion: To our knowledge, this is the first genetically diagnosed Cantú' syndrome caused by point mutation in *ABCC9* gene. This case broadens the ethnic diversity and clinical variety of Cantú' syndrome.

P2-192

Shox-Haploinsufficiency Intra-Familial Phenotypic Variability and The Impact On Final Height: Report of a Pedigree

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SHOX haploinsufficiency (SHOX-D) is a genetic cause of disharmonic short stature. However, the different impact on phenotype can show differences between patients with the same genotype.

GH ameliorates final height, with significant differences between patients for the putative role of environmental factors who can influence growth.

We describe the case of two sisters with SHOX-D (target height: 146.8 cm (-2.6SDS); mother: 146.5 cm; father: 160 cm). ZM was first evaluated at the age of 6.8 years for disharmonic short stature: stature: 103.5 cm; SPAN: 99 cm. She was affected by SHOX-D (heterozygous missense mutation *c414G>C: p.Glu138Asp* of the exon 3). The same mutation was first confirmed in the mother, and later in the sister who had not a stature < -2SDS at the first clinical evaluation. Both the patients did not show GH deficiency and IGF-1 levels were in the normal range.

GH treatment was started at 6.8 years for ZM (BA: 6 years): stature: 103.5cm: -3SDS; SPAN: 99cm; and at the age of 6.8 years (BA: 6.1 years): stature: 113cm: -1.38SDS; SPAN: 112.5cm; for ZS, when the patient showed a reduction of height velocity, despite the progression of BA. At the follow-up the patients showed increased growth velocity, progression of puberty and progressive increased BA, with an early near-adult height of ZM at 13.7 years of 143.1cm (-2SDS), SPAN 138.5cm, BMI 18 kg/mq; weight: 37.5kg (-2SDS); bone age: 18 years. ZS at the age of 14.4 years showed a stature of 150.8cm (- 1.8SDS), SPAN: 155cm; BMI 22 kg/mq; weight: 50kg (-1SDS).

This family shows a different phenotype of SHOX-D: the mother, spontaneously reached a stature of 146.5cm. The sisters started GH treatment at the same age, however they showed a different response. Bone age rapidly increased at puberty.

ZM, with the most severe phenotype, had a near-final height of 143.1cm, with a low SPAN. ZS reached a higher stature and a SPAN at this time higher than the stature.

This case series show that SDS of stature before GH therapy is a prognostic parameter for final height in SHOX-D patients.

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P2-193**Linear Growth of Children with Celiac Disease (CD) after the first two years on a Gluten-free Diet (GFD); A Controlled Study**

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We evaluated the effect of GFD on the growth of children with the classical form of CD on long-term GFD (> 2 years).

Methods: We studied growth parameters (weight gain/day, BMI and BMISDS, HtSDS) and lab data for 30 prepubertal children aged 8.5 years +/- 3 years with CD, who were on GFD since the age of 3.4 years +/- 2.6 years (> 2 years on GFD) for duration of 1 year. The anthropometric data of 30 randomly selected normal, age and sex-matched, children were used as a control.

Results: The weight gain per day was average or above average for age and sex in 27 children and below average in 3. Two out of those 3 children had slow linear growth (decreased HtSDS by -0.56 and -0.1 over one year). BMISDS was normal in 26 /30 patients (> -1.5). BMI SD changed from -0.36 +/- 1.1 to -0.33 +/- 1.1 during the year of treatment. BMISDS decreased in 9 children during the follow up period that can be explained by their fast-linear growth (increased HtSDS) in seven of them. The HTSDS was < -2 in four out of the 30 children at the beginning of F/U and in 2 children after a year of F/U (catch up in two), HTSDS remained normal or increased in 28/30 children during the year of treatment (-0.38 +/- 1.2 to -0.22 +/- 1.1), a positive trend = 0.15 +/- 0.4 SD. Only one patient crossed down 1 major height centiles during the year of follow up, with low weight gain/day and decreased BMISDS that can be explained by incompliance with the GFD. HtSDS and BMISDS increased significantly in the CD group versus controls during the year of follow-up. All patients had normal serum albumin, liver enzyme and hemoglobin levels. 33.3 % of patients had low Ferritin level and 33.3% Had Vitamin D deficiency.

Discussion: Most of our children with CD grew normally both in height and weight on GFD. Catch-up growth still occurs in some of them after 2 years of being on GFD. All had normal Hb and albumin level. Those with low BMISDS and/or HtSDS need further management including reinforcement on following strictly the GFD and investigating other factors that might affect growth pattern

Conclusion: Catchup growth continues in some children with CD on GFD even after 2 years of being on GFD. Measuring weight gain /day is a sensitive indicator for monitoring growth in these children.

P2-194**Growth hormone treatment adherence in patients from an emerging economy country: 1-year real-world data from the easypod™ connect eHealth platform**

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Previous studies have shown that poor adherence to recombinant human growth hormone (r-hGH; Saizen®) therapy is associated with decreased efficacy outcomes and increased healthcare costs. Easypod™ is the only electronic injection device that enables continuous monitoring of adherence to treatment. Early recognition of non-adherence is essential in the management of long-term outcomes of r-hGH therapy. This analysis aimed to evaluate adherence to r-hGH therapy administered via easypod™ up to 12 months in Brazilian patients.

Data from the past 48 months were downloaded on 15th February 2019 from easypod™ connect. The period of recorded data varied, according to individual's treatment length. Data were stratified by age, gender and device engagement. Patient adherence was calculated as mg Saizen® injected vs mg Saizen® prescribed and categorised as high [≥85%], intermediate [>56%–84%] or low [<≤56%]. Only data after the 10th injection registered were analysed. Puberty cut-off points were 10 years for girls and 12 years for boys.

In total, 984 patients recorded >10 injections. Overall, there were 750 patients (76.2%), 195 (19.8%) and 39 (4.0%) in the high, intermediate and low-adherence categories respectively. Although a slight decrease in adherence was recorded over time, 178 of 246 (72.4%) patients were still in the high-adherence category at month 12. After 12 months there was no difference in high-adherence rates between pre-pubertal (66/92 [71.7%]) and pubertal patients (112/154 [72.7%]). However, more girls had high-adherence rates than boys (78/103 [75.7%] vs 100/143 [69.9%]), and this difference mainly laid in the pre-pubertal group: girls (21/25 [84.0%]) vs boys (45/67 [67.2%]). The proportion of pubertal girls vs boys was comparable (57/78 [73.1%] vs 55/76 [72.4%]). Patients in the high-adherence category had the highest mean number of data transmissions at 12 months (6.4 [SD 8.4]) compared with the intermediate and low adherence categories (4.1 [SD 4.7] and 4.1 [SD 5.1]) respectively.

This is the first analysis of adherence exclusively in Brazilian patients using easypod™ connect in a real-world clinical setting. Overall, the majority of patients were in the high-adherence category. Adherence was higher in pre-pubertal females than males, but comparable in pubertal patients. After 12 months, 28% of patients were in low or intermediate categories, demonstrating that adherence is an issue that continuously needs to be addressed with families and patients. Through our validated method of recording adherence, we can address an unmet need in r-hGH therapy.

P2-195

The Clinical Features and Effect of Growth Hormone Treatment in 3-M Syndrome Cases with Severe Growth Retardation

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Background: 3-M syndrome is an autosomal recessive growth disorder characterised by severe prenatal and postnatal growth retardation caused by mutations in CUL7, ODSL1 or CCDC8. Clinical characteristics include dysmorphic facial features and skeletal abnormalities.

Aim: Evaluation of clinical and molecular findings and the effect of growth hormone (GH) therapy in seven patients with 3-M syndrome from five different families.

Patients and Methods: Clinical and laboratory findings of seven patients(4males,3females) from 5 different families[Family(F) I(Patient(P1,P2), FII(P3,P4),FIII(P5),FIV(P6),FV(P7)] were evaluated retrospectively. Pituitary function, GH stimulation and IGF generation tests were recorded. Growth and pubertal features were evaluated at follow-up.

Results: Median (range) age of the patients was 6.5(0.5-16.6) years, 4 males(P1, P2,P6,P7), 3 females(P3,P4,P5). There was consanguinity in three families(FI, FII, FIV). Six cases(85.7%) were low birth-weight SDS was -3.1[(-1.4)-(-5.1)]. All patients presented with severe growth-retardation; median (range) height SDS was -5.3[(-3.9)-(-7.9)], BMI SDS was -0.8[(-2.4)-(1.5)], head-circumference SDS was 1.4[(-0.17)-(-2.5)]. All patients had dysmorphic features related to 3-M syndrome. All patients' bone-age were delayed. CUL7 gene mutations were found in FI(homozygous;p.T731insGlufs) and FV(novel, compound heterozygous;p.Pro1511Ser/p.Arg1528Ter), ODSL1 gene mutations (homozygous;p.Thr425Asp) were found in FII and FIII. Family IV's molecular analysis has not been completed yet. GH response in stimulation tests were normal in P4,P5,P7, high in P1,P2,P3 and low in P6. Five patients except(P1 and P7) were started GH treatment. Median of GH treatment duration was 1.9 years(0.1-4.3). Response to GH treatment was insufficient in all five patients. Patient 1 was 16.6 years-old at presentation while his pubertal-stage was Tanner-II and delayed. At recent evaluation he was 18.6 years-old and pubertal-stage was Tanner-III and puberty has not completed yet. Patient 6's puberty started at age 13.5 however progressing slowly, evaluation at age 17.1 his pubertal stage was Tanner-III and hormone levels were indicating partial primary hypogonadism. Recently, all female patients and P7 are below ten years of age and prepubertal. P2 is 13.1 years-old and prepubertal.

Conclusion: 3-M syndrome should be considered in differential diagnosis of patients with severe prenatal and postnatal growth retardation. Children with 3-M syndrome are treated with GH but there is lack evidence of efficacy in literature. Insufficient response

to GH treatment and high levels of GH in tests might indicate GH resistance and IGF1 receptor resistance. 3M syndrome might cause delayed puberty and partial primary gonadal insufficiency in boys.

P2-196

Klinefelter Syndrome Associated with Short Stature due to Iatrogenic Cushing

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Introduction: Klinefelter syndrome (KS) is a form of aneuploidy resulting from 2 or more X chromosomes in a male. The most common karyotype is 47,XXY. KS affects physical and intellectual development to varying degrees, commonly causing hypo-development of secondary sexual characters and high stature.

Case Report: JLV, male, 3 year 1 month age, the first child of a young non-consanguineous couple, was referred to the pediatric endocrinology department with Short Stature (SS) main complaint. The mother's height is 158cm, and the father's height 178cm (Target height 174.5cm).

He had clinical history of atopic dermatitis and allergic rhinitis, and because of these diagnosis the patient used during the last year: nasal beclomethasone (twice a day), nasal fluticasone (three times a day), topical hydrocortisone on the scalp (once a day) and oral methylprednisolone during periods of wheezing. All drugs were prescribed by doctors.

Physical examination revealed the increase of lanugo throughout the body and syndromic facies: retroverted small ears with low implantation, ocular hypertelorism, wide nasal base, oval palate. Normal segmental examination, G1P1. 90.5cm (- 1.99 SD) and 10kg (- 3.17 SD).

General biochemical tests, thyroid, renal and hepatic functions were normal. Basal ACTH was 6.2 pg/ml (Normal range: 7.2 - 63.3 pg/ml), basal cortisol was 5.7 mcg/dl and one hour after cortrosin (synthetic ACTH) was 18.7 mcg/dl.

The child was referred to an allergist who introduced other classes of medications, enabling glucocorticoid withdrawal and posterior recovery of growth rate.

Blood karyotype with Band G: 47, XXY

Conclusion: The systemic manifestations of prolonged exposure to glucocorticoids are widely reported; however, iatrogenic Cushing Syndrome (CS) is very common. In this case CS was able to mask one of the striking features of the KS carriers, which is high stature.

We observe the delay in the diagnosis of KS and the induction of CS due to poor medical practice. The prescription of glucocorticoids should be judicious: precise indication and for a determined time in prescription, adequate dosage and clear orientation to the patient about the risks of the occurrence of CS with the indiscriminate use.

This case exemplifies how essential it is for every physician to value the clinical method, based on thorough anamnesis and physical examination, aiming for the patient's well being

P2-197

Extending the phenotype and genotype of Okur-Chung neurodevelopmental syndrome

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Background: Okur-Chung neurodevelopmental syndrome was confirmed to be associated with developmental disorders attributed to germline CSNK2A1 pathogenic missense variants. Only 26 cases and 22 kinds of genotype have been reported in the world so far. All reports highlighted the recognizable facial features of the syndrome as well as frequently occurring clinical features including neurodevelopmental delay, short stature, gastrointestinal, musculoskeletal and immunological abnormalities.

Aim: The main objective of this study is to report a case of Okur-Chung neurodevelopmental syndrome and extend the phenotype and genotype of this disease.

Methods: We report a 8-year-old Chinese boy, analysis of the patient clinical phenotype and genotype. Exome sequencing was performed for the patient and his parents (trio). The gene mutation in our patient was confirmed by Sanger sequencing.

Results: The boy was born as the first child of a healthy mother and father. Due to fetal hip circumference, prolonged labor, choose cesarean section. His birth measurements were: weight 3110 g (+0.2 s.d.), length 48.0 cm (-1.2s.d.) and OFC 34.0 cm (-0.2 s.d.). Microcephaly became evident in the first 3 years of life. The motor development and speech development were both delayed. At last examination at age 8 years, the patient presented with global developmental delay, intellectual impairment, borderline microcephaly, arched eyebrows, Low set ears, brachycephaly and dysmorphic features. He was short stature, epilepsy and hypermyotonia. The functions of the thyroid gland and pituitary gland were normal. We observed that the CSNK2A1 gene is relatively intolerant to missense genetic changes, CSNK2A1 c.149A>G(p.Tyr50Cys) is located in the active site of protein and the aspartate residue at position 50 is also highly conserved.

Conclusion: Okur-Chung neurodevelopmental syndrome can cause short stature, facial features and neurodevelopmental delay etc. Last reported motion abnormality was hypotonia. In our case the motion abnormality was hypermyotonia. We also found the gene mutation CSNK2A1 c.149A>G(p.Tyr50Cys) was maybe a de novo mutation. This case report can extend the phenotype and genotype of Okur-Chung neurodevelopmental syndrome.

P2-198

Evaluation of Diagnosis, Follow-up and Treatment

Results of Growth Hormone in Rare Diseases; 10 Year Single Center Experience

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Introduction: Growth hormone therapy (GHT); have been used in rare diseases such as growth hormone deficiency (GHD), panhypopituitarism (PHP), intrauterine growth retardation (IUGR), Turner Syndrome(TS) for many years while the effects of diagnostic timing on the treatment results are known. However, data on the diagnosis and treatment processes of these diseases are limited in our country. The aim of this study was to evaluate the results of diagnosis, follow-up and treatment of the patients who were started GHT for the last 10 years and to determine the differences in the process and results over the years.

Materials and Methods: 857 patients who underwent GHT between 2009-2018 were evaluated retrospectively in all patients and subgroups(GHD, PHP, IUGR, TS) in terms of GHT onset time, follow-up, GHT offset time, anthropometric, clinical, laboratory data, treatment adherence and side effects.

Results: GHT was started in 695 cases (81.1%) with GHD, 24 (2.8%) with PHP, 26 (3%) with IUGR and 28 (3.3%) with TS. The median age of onset of GHT was 12.2 years and the earliest was on IUGR (8.6 years) on the other hand, it was at the latest on GHD (12.3 years). In 17% of patients, treatment was interrupted due to adjustment problem, low growth rate and IGF1 increase. Side effects were seen in 3% of the patients (significant elevated CK, scoliosis, cardiac causes). At the time of treatment offset, height SDS in GHD and PHP were significantly higher than treatment onset time, whereas there was no significant difference in TS and IUGR. 218 cases reached the final height. Final lengths in boys/girls were respectively in GHD:153/164,1cm PHP:155,6/162,7cm; TS:147,2cm(133-156.4); IUGR:144.6 (136.7- 150.3), respectively. Of the 166 GHD patients who reached their final height, 104 (67.5%) were found to reach their target height.

Conclusion: In this study, 81.1% of 857 patients who had undergone GHT were treated with the diagnosis of GHD, no difference was observed in the last 10 years between the age of presentation and treatment of the patients and the treatment was started late. The patients' compliance with treatment was high (91%) and the incidence of side effects was low(3%). Approximately 68% of 166 GHD cases reached the target height. Considering the findings of our study, it was concluded that due to short stature in our country, age at admission and onset of GHT were late and there is a need for more studies on this subject.

P2-199

Growth failure in children with sickle cell anemia

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Sickle cell anemia (SCA) is the most common subtype of sickle cell disease (SCD) worldwide. The disease is highly prevalent in Sub Saharan Africa with a prevalence rate of 3% in Nigeria; a country with a population of over 180 million. Growth failure is a recognized clinical feature in SCA patients which culminates to short stature if unaddressed. Late presentation/age at diagnosis is one of the daunting challenges. Despite the high prevalence of children with SCA in West Africa, there is paucity of report on the prevalence of growth failure in SCA patients. Hence, the compelling need to embark on this study. The aim of the study is to determine the prevalence of growth delay/failure in Nigerian children with SCA and its relationship with age at diagnosis.

Methodology: A prospective, longitudinal study of consenting children and adolescents with SCA in attendance at the Haematology clinic of the Department of Paediatrics, University of Nigeria teaching hospital [UNTH]Enugu, Nigeria over a period of one year. The age at diagnosis was obtained. Their heights were measured at three monthly intervals and plotted on a standard WHO growth chart. The parental heights were measured for mid parental height calculations. The height velocity (HV) was calculated using the different height values obtained from the three-monthly interval measurements over a year period. HV was compared with the WHO standard normal linear growth rates for children to identify those with growth failure.

Results: A large cohort of 287 children with SCA were evaluated with a male preponderance of 161 [56.1%]. The mean age of participants was 10.4 years and the mean age at diagnosis was 4 years. 54.7% of the children with SCA had Height velocity standard deviation {HVSD} of below -1 during a full year linear growth. An inverse correlation existed between age at diagnosis and height velocity (p value <0.05)

Conclusion: The study demonstrated high prevalence of growth failure in children and adolescents with sickle cell anemia SCA which worsens with older age at diagnosis.

P2-200

Endocrine Features of Schaaf-Yang syndrome. Case report

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Background: Schaaf-Yang syndrome is caused by heterozygous mutation in the MAGEL2 gene (605283) on chromosome 15q11. Schaaf-Yang Syndrome is an autosomal dominant multisystem disorder characterized by psychomotor and mental retardation, hypotension, and behavioral abnormalities. Additional signs include joint contractures, feeding difficulties and various

dysmorphic features. The severity of the disorder varies greatly: some patients may live with moderate disability. Individual lesions occur only if the mutation occurs in the paternal allele, since MAGEL2 is a gene imprinted on the mother. Here we report a case of Schaaf-Yang Syndrome with endocrine features.

Case Report: Manifestation was at birth. A boy appeared to have disproportionately small hands and feet, dysmorphic facial features, esotropia and micrognathia. The patient was lethargic with no interest in feedings and poor suck/gag reflex. He was placed on feeds through a nasogastric tube. His laboratory workup was significant for hypoglycemia and hypocalcemia. On the first day of life, an MRI showed Grade I intraventricular hemorrhage bilaterally and a hemorrhage within the pituitary gland. His EEG showed bitemporal sharps and complexes concerning for subclinical seizures. At the age of 3 months boy had feeding difficulties with poor suck, muscle hypotonia, vomiting, failure to thrive, spasticity, generalized seizures, encephalopathy, optic atrophy, pachygryria, bulbar syndrome, congenital malformations of the osteoarticular system, camptodactyly, abnormal urinary system and external genitalia, hypogonadism.

His parents are non-consanguineous and asymptomatic. They have no further affected child. Laboratory: hypoglycemia: serum glucose 2.3 – 2.9 mmol/l, C-peptide 0.41 – 0.44 ng/ml (0.7 – 1.9). HbA1c – 4.6% insulin – 7,02 mcU/ml (2,0 – 25,0). TSH – 3.27 mIU/L, FT4 – 16.67 pmol/L, FT3 – 4.77 pmol/L, IGF-1/IGF-BP3 – normal, PTH – 38.58 pg/ml (15-68). Screening for other endocrine dysfunctions was negative. Blood calcium – 2.48, ionized calcium – 1.21, phosphorus – 1.84 mmol/l. Total VitD (D2+D3) – 48,84 ng/ml (sufficient level 30 – 80). Total protein – 63 g/l. Ammoniak – 23.0 mol/l (15-70). Uric acid – increase. IgA anti-tissue transglutaminase antibodies – normal level, gliadin – 0.10 kU/L, kasein DPC – 0.31 kU/I. Zink – 15.3 mcmol/L (9.8 – 16.8), iron – 13.81 mcmol/L, magnesium – 1.0 mmol/L, copper level – 11.3 mcmol/l (10-22). Folic acid – 45.4 nmol/L (10.4 – 42.4). The genetic diagnosis of Schaaf-Yang syndrome is confirmed: MAGEL2 (NM_019066.4, sequencing, heterozygous variant c.1996dup p.(Gln666Profs*47).

Conclusion: Given the seriousness of the results, we strive to describe the early abnormalities in the endocrine status of a child with the unique phenotypic features of the MAGEL2 mutation, which determine clinical suspicion and early intervention to manage its complex manifestation.

P2-201

Papillary thyroid cancer in a 17-years old girl with a late-diagnosed Turner syndrome

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Background: Papillary thyroid cancer has been described in three patients with Turner syndrome (TS) who received growth hormone therapy (Cabanas P, 2005; Bautembach-Minkowska J, 2018). We are presenting a case of papillary thyroid cancer in a girl with a late-diagnosed Turner syndrome who has not received any hormonal therapy up to 17 years.

Clinical case: A girl was diagnosed with TS syndrome (karyotype 45XO/46X i(X)q) at the age of 17 years old. Objectively, the girl had a short stature (height 141 cm, SDS = -3.5), hypergonadotropic hypogonadism, bone age was 15 years old, and there were no heart or kidney defects. Until now, the patient has not received any hormonal therapy. Family history towards thyroid disorders and ionising radiation was negative. During the exam, Hashimoto thyroiditis was detected (with normal level thyroid stimulating hormone (TSH) 2.2 mU/ml (0.35-4.92), normal level free thyroxine (free T4) 16.9 pmol/l (9.1-21), high levels of antithyroid peroxidase antibodies (anti-TPO) 1000 IU/ml and thyroid thyroglobulin antibodies (anti-Tg 150 IU/ml [< 115]. On the ultrasound a hypoechogenic nodule ($1.0 \times 0.9 \times 0.9$ mm) was seen in the left lobe of the thyroid gland with microcalcinates and vasculature on the border. Fine needle biopsy was provided and the cytological exam revealed a structure of thyroid cancer (Bethesda V). The patient was immediately performed total thyroidectomy with lymphadenectomy, including removal of central lymph nodules of the neck and about thyroid isthmus and both lobes. The histopathology of the removed tissue of nodule revealed a structure of classical papillary thyroid cancer. The stroma of the thyroid was characterised by colloidal goitre and multifocal reactive lymphoplasia. Central lymph nodules of neck were free from cancerous tissue. The performed surgical treatment was accepted as completed, suppressive therapy with levothyroxine was initialized (125 mcg per day). There was no recommendation for therapy using ^{131}I at present. After surgery hypoparathyroidism was detected (low ionised calcium level – 0.9 mmol/l [1.05-1.30] and low concentration of parathormone in serum – 2 pg/ml [16.00-87.00], girl was prescribed replacement therapy with alfalcacitol and calcium with a positive effect.

Conclusions: We have presented a case of papillary thyroid cancer in a girl with late-diagnosed TS without any hormonal therapy to 17 years old. She had autoimmune thyroiditis, which is a risk factor for the development of this condition.

P2-202

The applicability of the NH-Clinical scoring system on diagnosis of Iranian children with SRS

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Background: Silver Russell Syndrome(SRS) is a rare heterogeneous genetic disorder, which is mostly known because of its prenatal and postnatal growth retardation. Patients with Russell silver syndrome have syndromic facial appearance as well as some other common clinical features. The last guideline for diagnosis of SRS is Netchine– Harbison clinical scoring system that is clinical scoring system and followed by molecular evaluation.

Objective: In Silver Russell Syndrome, evaluating loss of methylation on 11p15 and maternal uniparental disomy for chromosome 7 (upd(7)mat) are most common molecular changes which

can be assessed in such patients.In our first phase of our study we evaluated Netchine– Harbison clinical scoring system(NH-CSS) for children with clinical features of SRS . In the second phase we evaluated molecular MLPA testing of methylation on 11p15 region in 15 patients with positive diagnostic NH-CSS criteria.

Patients: This case series has been approved by Mashhad University of medical sciences committee, Mashhad, Iran. Every children who were presented with clinical diagnosis of Russell silver syndrome and were younger than 20 and older than 2 years old were referred to pediatric endocrinology department for further evaluations. Among children who were referred, only 16 patients were confirmed to have Russell silver syndrome clinically according to Netchine–Harbison clinical scoring system. According to this criteria, clinical diagnosis has been made if a children scores at least 4 of 6 clinical criteria's including: small for gestational age, postnatal growth failure, relative macrocephaly at birth, body asymmetry, protruding forehead and feeding difficulties and/or low body mass index. Other possible differential diagnosis has been excluded according to children features and those who were not willing to undergo molecular evaluation or disagree for filling the informed consent form were excluded. Total number of 16 children agreed to enrolled in present study and undergo molecular evaluation.

Result: From 16 patients who had diagnostic SRS in the basis of NH-CSS criteria, 5 cases had positive MLPA testing(31.25%), that is compatible with other studies in different regions(30-60%). It seems that NH-CSS criteria is a perfect and appropriate guideline for initial evaluation of those short stature patients who are suspected of SRS. (The molecular analysis article has been approved in iranian journal of pediatric and it will be published soon).

Multisystem Endocrine Disorders

P2-203

Clinical Manifestations & Molecular analysis of Thirteen Palestinian Families with Sanjad Sakatti Syndrome revealing a common deletion founder effect and another two novel mutations

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Objectives: Sanjad-Sakatti syndrome or hypoparathyroidism-retardation-dysmorphism syndrome (HDRs) is a rare autosomal recessive multisystem disorder characterized by intrauterine and postnatal growth retardation, infantile-onset hypoparathyroidism that can result in severe hypocalcemic seizures, dysmorphic facial features, and developmental delay.

Methods: Thirteen unrelated Palestinian infants to a consanguineous Palestinian families presented in early infancy with hypoparathyroidism, hypocalcemic seizures, dysmorphic features, growth retardation and developmental delay, assessed to have Sanjad-Sakatti syndrome and were managed accordingly. Clinical manifestations of all presenting patients and their molecular analysis has been checked to correlate clinical presentation with the specific genotype.

Results: Sequencing of the TBCE gene showed that ten patients of our series of Thirteen patients are homozygous for the mutation (c.155_166del12;p.del52-55) in exon 3 of this gene, the common deletion founder effect of the TBCE gene in Arab patients, while the other three patients had novel mutations:c.355_356delAT in exon 4 of TBCE gene and c.354_355del, p.S118fs of the TBCE gene (which has been detected by whole exom sequencing).

Conclusions: To our knowledge, this is the first description of a series of thirteen families of Palestinian origin of this disease with molecular confirmation, showing the common deletion founder effect, allowing accurate genetic counseling, early diagnosis of affected kindred-s, early therapeutic interventions and avoiding complications. Checking novel mutations for this disease, allowing to check if the clinical presentation does correlate well with the specific genotype in Palestinian patients.

P2-204

Electromagnetic fields exposure in Adolescents: a survey in 11-14 y old Greek students

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Background: Electromagnetic field (EMF) exposure has been considered a potential environmental toxicant, which may influence endocrine and other functions, while population awareness remains limited. In an earlier study, we demonstrated that EMF alters the hypothalamic-pituitary-adrenal axis in children using a 3G mobile telephone.

Aim: To screen and compare the motives, knowledge and status of electromagnetic field exposure in Greek pupils aged 11-14 years.

Methods: A specifically designed survey, including a 4-point Likert scale for 35 statements grouped under six dimensions (demographics, mobile phone possession, medical history, risk perception, mobile phone use self-reporting, information of domestic exposure, residence vicinity to other external sources of exposure (base stations, electric power lines) was constructed. Some of the questions were addressed to the parents. The determinants were analyzed by regression analysis. Reliability was computed using the Cronbach's alpha coefficient and size of the effects was evaluated by the Odds ratio coefficient.

Results: 363 pupils (healthy except 8) and their parents answered the questions. Females and males were even, while, mobile telephone owners vs non-owners were 3:1. Non-owners reported scarce use. The Cronbach's alpha coefficient of the overall 20 items was 0.78, and 0.79, 0.71, 0.58, 0.73, 0.65 and 0.67 for the six dimensions, respectively. Users increased with age, family's socio-economic status and parental education (p trend <0.05), whilst, girls showed talkativeness. Additionally, families ignored potential exposure sources surrounding them.

Conclusions: Population education strategies, as well as future risk assessment studies, may benefit from information extracted from detailed age-specific surveys.

P2-205

Subcutaneous ossifications in children - think about AHO!

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Background: Pseudohypoparathyroidism (Albright hereditary osteodystrophy (AHO)) is a rare congenital disorder mainly affecting bone and thyroid metabolism as a result of resistance of parathyroid hormone (PTH) and thyrotropin (TSH), gonadotropins, growth hormone-releasing hormone (GHRH) and calcitonin in the target tissues. According to the consensus statement "Diagnosis and management of pseudohypoparathyroidism and related disorders" published in 2018, the specific diagnosis is often delayed owing to lack of recognition of the syndrome and associated features.

Case presentations: A two year old boy was seen with early onset obesity and motor delay. At the abdominal skin lividly discoloured lesions were seen. Another unrelated eight months old boy presented since the age of five months with early onset obesity, intracutaneous calcifications and mild motor delay. In both children we found high parathyroid hormone serum levels (442 pg/mL and 88 pg/mL, normal range: 11-67 pg/mL) in combination with elevated levels of TSH. In both patients sequencing revealed a heterozygous mutation c.565_568delGACT; p.ASP189Met*14 in the GNAS gene. This particular mutation has already been described and confirmed the diagnosis AHO. Levothyroxine and calcitriol treatment as well as physiotherapy were immediately started.

Conclusion: Subcutaneous ossifications combined with motor delay and early onset obesity may often be the single clinical signs of pseudohypoparathyroidism. Paediatric endocrinologists should therefore advise their paediatric colleagues about this syndrome and its clinical picture and motivate them to transfer these patients to a paediatric endocrine centre for further management.

P2-206

Growth outcomes in growth hormone treated Indian children with celiac disease

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Objective: To evaluate the height outcomes with growth hormone (GH) therapy during gluten free diet in celiac disease (CD) associated with growth hormone deficiency in associated with isolated GHD.

Method: A retrospective study of 17 CD with growth hormone deficiency with 17 age and sex matched children with GHD were included in the study. Their pre and post treatment height and predicted height were evaluated.

Results: On analysis the mean weight in GHD was 28.7kg, CD was 28.37kg and the GHD group was shorter (124.67cm) at start

than the CD group (128.46cm). The height velocity was better in the GHD group (10.3cm/yr), and 8.03ccm/yr in CD which was statistically significant. The mean predicted final height was better in the GHD 161.3cm and 158.1cm in CD. The Z score of PAH in GHD was -0.15 (SD 1.077), and in CD was -0.56 (SD 0.81) this was significant ($p<0.001$). The weight in GHD was 28.7kg and in CD was 27.3kg, but the final mean weight after treatment was 35.6kg and in CD was 43.6kg($p<0.03$)

Conclusion: GHD and CD is a rare association and this is the first study from India analyzing the association with comparisons of the growth outcomes.

P2-207

Functional ovarian and thyroid disturbances in a group of adolescents with insulin dependent diabetes mellitus and vitamin D deficiency

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Aim of the Study: Assessment of the incidence of ovarian functional disorders correlated with thyroid disorders appreciated clinically, functional, and echostructural in a group of diabetic female teenagers according to 25-(OH)- vitamin D serum levels.

Method: A group of 31 patients with diabetes mellitus and vitamin D deficiency (mean age 16.3 ± 1.3) was studied compared to a control group (43 teenagers) with diabetes and a normal vitamin D level, (mean age 16.7 ± 0.8). In all cases, diabetes mellitus was diagnosed and treated from the prepubertal period.

We evaluated the characteristics of the ovarian cycle, the development of sexual characteristics, serum levels of ovarian and gonadotrophic hormones, thyroid changes as measured by clinical and ultrasound examination as well as the measurement of free- thyroxine (FT4), thyrotropin (TSH) and serum 25-(OH)-vitamin D.

Results: Menstrual disorders occurred in 77.4% of adolescents with diabetes and low vitamin D, compared with 24.4% among adolescents in the control group. Changes in serum levels of ovarian hormones were significantly more common among patients with diabetes mellitus and vitamin D deficiency (77.4%) than the control group (31.3%). Ovarian hormonal changes were the progesterone deficiency (83% / 68%) and hyperprolactinemia (23% / 9.3%). The incidence of goiter (26.3% / 11.8%) and thyroid volume (14.3ml / 9.8ml) were higher among the patients with diabetes and low vitamin D. Thyroid functional disorders were recorded in 4 teenagers in the study group: 3 cases with subclinical hypothyroidism and 1 case with overt hypothyroidism. The positivity of anti-thyroid autoantibodies was present in 29% of teenagers with low vitamin D versus 2.4% of teenagers in the control group. The study was conducted in the perimarine area of Romania known to have a maximum annual sunny period compared to the rest of the country.

Conclusions: Vitamin D deficiency associated with insulin dependent diabetes mellitus in puberty appears to be a factor with an aggravating role in the development of ovarian and thyroid disorders appreciated clinically, echostructural and functional.

P2-208

Autoimmune polyendocrine syndrome type I: A neuroendocrine multi-systemic disease with a variable expressivity

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Introduction: Autoimmune polyendocrine syndrome type I (APS-1) also called autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a rare monogenic autosomal recessive disease known by the triad of the major components hypoparathyroidism, primary adrenocortical insufficiency and chronic mucocutaneous candidosis. However, many minor diseases could be present such as other endocrine manifestations (gonadal insufficiency, DM type 1, thyroid disease, pituitary failure), gastrointestinal manifestations (autoimmune gastritis, autoimmune hepatitis, intestinal dysfunction), ectodermal manifestations and others.

Patients and Methods: two siblings affected by APECED with the same genotype (AIRE 260 T>C; 967-979 del) and extremely different phenotypes were compared. Hypoparathyroidism and alopecia were the only two components they have in common. Both siblings have been treated for > 5 years with off label rh-Teriparatide treatment with a good response of calcium levels. The girl (patient 1) showed growth and pubertal delay, vitiligo and ectodermal dystrophy. At the age of 12 chronic diarrhea, abdominal pain and malabsorption appeared. Esophagogastroduodenoscopy showed autoimmune enteropathy characterized by the loss of enteroendocrine cells (EEC) in the gastrointestinal tract. An experimental immunosuppressive therapy with oral Budesonide improved symptoms.

Conversely the brother (patient 2) showed a different phenotype: hypoparathyroidism, primary adrenocortical insufficiency and alopecia were present. Replacement therapy with mineralocorticoid (fludrocortisone) and glucocorticoid (hydrocortisone) was necessary. No growth nor pubertal delay and gastrointestinal symptoms were revealed.

Conclusion: APECED is a multi-systemic disease and it requires a multidisciplinary approach. Hypoparathyroidism can be treated with rh-Teriparatide which seems to be a safe and an effective long-term therapy. Replacement therapy is also necessary when adrenal insufficiency appears. Chronic diarrhea may be due to several causes such as pancreatic exocrine insufficiency (PEI), autoimmune enteropathy (AE), lactose intolerance and celiac disease as well as the same hypocalcemia. Loss of EEC cells determine the reduction of neuroendocrine hormones and consequently gastrointestinal dysfunction. In this condition immunosuppressive therapy is necessary but there are few data in literature so far.

Therefore, although APECED is a monogenic disease, its expressivity may be extremely wide even harbouring the same genotype within the same family. Major components are well known but "minor" components have to be readily recognized with a continuous follow up because they can have important effects on growth and quality of life.

Keywords: Autoimmune polyglandular syndrome type 1, APECED, phenotypic variability, enteroendocrine cells, rh-Teriparatide.

P2-209

Endocrine complications of patients with hepatic type of glycogen storage disease

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Background: Glycogen storage disease (GSD) is an inherited metabolic defect of metabolic defect of glycogenolysis and gluconeogenesis. Patients with GSDs are associated with endocrine abnormalities such as short stature, delayed puberty, fasting hypoglycemia, and dyslipidemia. In addition, patients with GSD 1b are also at risk of autoimmune hypothyroidism. Therefore, this study was performed to investigate endocrine complications in patients with GSD.

Methods: This study included 55 patients from 46 families diagnosed between January 1995 and December 2017: GSD type Ia (37 patients from 34 families), Ib (n=3), III (six patients from 4 families), IV (n=1), and IX (8 patients from 4 families). All patients were genetically confirmed by Sanger sequencing of the causative genes. Patients with muscle glycogenosis were excluded in the study. Clinical and endocrine characteristics were retrospectively analyzed such as height, weight, hypoglycemia, lipid profiles, and bone mineral density.

Results: The median age at diagnosis was 2.4 years (range 0.4 to 42 years). The mean height SDS at diagnosis was -1.84 ± 1.88 (range -8.31 to 1.44). Short stature (height SDS <-2 SDS) was prevalent in GSD Ia (18/37 patients, 48.6%). The current median age was 16 years (range 0.9 to 47.8 years), and the mean height SDS at current age was -1.45 ± 1.59 (range -7.46 to 1.34). The mean triglyceride level was 520 ± 448.3 mg/dL at diagnosis and decreased to 346.3 ± 390.5 mg/dL at last-follow-up ($P = 0.0408$). Thyroid functions were analyzed in 24 patients, resulting in within the normal reference range in all patients. Vitamin D deficiency (25-hydroxyvitamin D₃ <20 ng/mL) was found in 15 of 37 patients (40.5%). Dual-energy X-ray absorptiometry analysis was performed in 16 patients. As a result, osteoporosis (bone mineral density Z score <-2 SDS) was documented in 11 patients.

Conclusions: This study demonstrated that the patients with GSD type Ia developed significant growth retardation. In addition, other endocrine abnormalities such as dyslipidemia, osteoporosis, vitamin D deficiency can be associated in the patients. Dietary treatment with uncooked cornstarch improves growth and partially corrects the biochemical findings. Future longitudinal studies with a large number of patients may allow better understanding of factors that impact endocrine complications.

P2-210

Autoimmune Thyroiditis and Autoimmune Hepatitis presenting at onset of Type 1 Diabetes (T1D)

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Background: Autoimmune disease (AD) occurs due to loss of immunological tolerance to self-antigens and can be organ specific or systemic. One in four patients with a single AD may develop another AD. The presence of three or more AD is described as multiple autoimmune syndrome (MAS) in which Type 3 subset includes autoimmune thyroiditis and T1D, but not autoimmune hepatitis. Type 2 Autoimmune Polyendocrine Syndrome can be diagnosed when T1D and autoimmune thyroiditis coexist. The association of autoimmune thyroiditis and T1D is well recognised but the co-existence of autoimmune hepatitis is unusual and the co-presentation of all three diseases, to our knowledge, has not been reported.

Case Presentation: 7-year old Caucasian female referred with a 2 week history of weight loss, polyuria and polydipsia. Investigations confirmed T1D with blood glucose 27 mmol/L, blood ketones 4.0mmol/L and normal pH 7.36. Anti-GAD antibodies were >2000 and HbA1c was 105 mmol/mol (20-41). Thyroid function tests were abnormal (TSH 8.07 (0.35-4.94mU/L), Free T4 14 (9-20pmol/L), TPO Antibodies >3000). Thyroid ultrasound revealed abnormal echogenicity, confirming autoimmune thyroiditis. Coeliac screen was negative. Short synacthen test was normal. Unexpectedly, liver enzymes were raised (ALT 1297 (<41U/L), AST 1616 (<37U/L), GGT 156 (<45 U/L)) as were IgG and IgM Immunoglobulins (27.3 (4.9-16.1g/L) and 3.77 (0.5-1.8g/L) respectively). Clotting, viral serology, alpha-1 antitrypsin, caeruloplasmin, serum copper and abdominal ultrasound scan were normal. Anti-neutrophil cytoplasmic antibodies were positive with elevated Proteinase 3 Antibody (21.27 (<3.5U/ml)) and low complement C4 (0.11 (0.14-0.54g/L)). Anti-liver/kidney microsome antibody (anti LKM) and antibody to liver cytosol (anti LC-1) were both positive. Liver biopsy revealed features in keeping with severe acute hepatitis. Given high IgG and positive liver autoantibodies, autoimmune hepatitis was diagnosed. She was commenced on a Basal/Bolus insulin regime for diabetes control, Levothyroxine for thyroiditis and Prednisolone daily for 8-12 weeks for autoimmune hepatitis. Liver function was monitored weekly with a weaning steroid plan. Her insulin requirement has increased markedly because of steroids, consequently her diabetes monitoring and follow up has been increased given the expected ongoing impact.

Conclusions: This case highlights the need for clinicians to have a low threshold for investigations into other AD (dependent on clinical features) when one AD already exists. National guidelines advise performing screening tests for autoimmune thyroiditis and coeliac disease in patients with newly diagnosed T1D. This case raises the question of whether further autoimmune conditions should form part of this initial screening.

P2-211

Ulnar mammary syndrome - a case report

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Introduction: Ulnar mammary syndrome (UMS) is caused by a mutation of T-box transcription factor 3 (TBX3). It is a rare condition with only a few cases being reported in the literature. We report a child with ulnar mammary syndrome.

Case Report: The patient presented to us at 14 years 6 months of age with concerns of failure to gain height which was noted from the age of 11 years. His investigations were suggestive of growth hormone deficiency, hygonadotropic hypogonadism. Genetic testing revealed heterogenous 5'splice site variation in intron 2 of the TBX3 gene that affects the invariant GT donor splice site of exon 2. The observed variation has previously been reported in a patient affected with ulnar mammary syndrome.

Discussion: Ulnar-mammary syndrome (UMS) was first described in 1975 by McKusick. UMS presents with high variability and typically with asymmetric presentation. It is a rare genetic disorder and the exact prevalence currently is unknown with less than 150 cases being reported in the medical literature. It is caused by a mutation in the T-box genes, specifically T-box transcription factor 3 (TBX3) on chromosome 12q23-24 which are involved in body patterning during embryogenesis and maps the extremities. A high index of suspicion is required to diagnosed this condition. Genetic test can be asked for when the clinical picture is not classical of the condition to confirm the diagnosis. Early diagnosis is important to treat the multiple co existing endocrine abnormalities and improve the quality of life in children with this condition.

P2-212

Unusual ovary formation in a girl with McCune-Albright syndrome

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McCune-Albright syndrome (MAS) is a rare disorder caused by somatic mutations in GNAS gene leading to fibrous dysplasia (FD), cafe-au-lait spots and hyperfunctioning endocrinopathies. The common feature of MAS in girls is peripheral precocious puberty (PP) with the recurrent ovary cysts. Few cases of ovary tumors have been described to date.

8,5 year-old girl with MAS is closely observed in our centre since the age 4,5, when the diagnosis was established based on the combination of FD, cafe-at-late spots and PP with recurrent ovary cysts. Throughout the 4-year-long period of follow-up she hasn't developed another features of MAS. She has FD of lower extremities with one fracture of the left fibula occurred at the age of 4,5. There is no visual deformities but according to x-ray assay the condition of the affected bones are getting worse with years. She had few episodes of vaginal bleeding because of the ovary cysts that had

been persisting for the period no longer than a month. At the age of 8,5 her height was 141,2 cm (SDS +2,16), Tanner P1B2, last vaginal bleeding occurred one year ago. During the annual screening for MAS features ultrasound signs of solid formation of the right ovary were found. Results of MRI confirmed existence of the large ovary tumor (4.5x4.3cm) with free fluid in the pelvis. At that moment estradiol was 63 pmol/l, basal levels of LH and FSH were low, central PP was excluded after performing GnRH agonist stimulation test, oncomarkers for ovarian cancer were all low. Since MRI results showed the tumor suspicious for disgerminoma the initial plan was to perform surgical treatment. But when control ultrasound was made after 9 days of the first one, there were no signs of the tumor and the second MRI revealed significant decrease in tumor size and disappearing of the ascitis. Close medical observation with regular pelvic ultrasound was recommended.

In MAS patients it can be difficult to establish treatment approach to the ovary formation, considering tendency to ovary cysts on the one hand and possibility to develop ovary tumors on the other.

P2-213

Heart rate variability in adolescent polycystic ovary syndrome Greek patients

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Background: The polycystic ovary syndrome (PCOS) is believed to contribute to adverse cardiovascular effects.

Aim: The aim of the present study was to investigate the potential alterations in heart rate variability (HRV) pattern in adolescent patients with polycystic ovary syndrome (PCOS).

Methods: Nineteen PCOS adolescent patients group (mean age 16.8 ± 3.2 years) and twenty one age- and body mass index-matched non-patients (mean age 16.9 ± 2.1 years), who presented to the Centre for Adolescent Medicine and UNESCO Chair on Adolescent Health Care of the First Department of Paediatrics, at the "Aghia Sophia" Children's Hospital, in Athens, Greece, over a period of one year, enrolled this study after informed consent signing. HRV was assessed by mean normal-to-normal beats intervals (mNN).

Results: Significant differences in mNN ($p=0.021$), between patient and control groups, was calculated.

Conclusions: HRV decomposed in mNN reflects the variance in time between consecutive sinoatrial depolarizations. The observed significant increase reflects specific shifts in sympathovagal balance; the observation may be disease specific, due to the androgen increased levels.

P2-214**Celiac disease and endocrine autoimmunity in children and adolescents**

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Objectives: Celiac disease (CD) is a life-long inflammatory disease of

the gastrointestinal tract that affects genetically susceptible individuals and is associated with several autoimmune diseases. The aim of the study was to evaluate the prevalence of coexistent autoimmune endocrine disorders in children and adolescents diagnosed with CD.

Patients and Methods: Children diagnosed with CD in the Paediatric Gastroenterology Outpatient Clinic of the General University Hospital “Attikon” were included in the study. Data were retrospectively reviewed. They were 62 patients, 48 girls, and 14 boys with a median age at diagnosis 9.0 years (range 2-17)

Results: 12.9% of children presented with positive antithyroid antibodies, a percentage significantly higher compared to the reported in the greek pediatric population (4.3%). Diabetes type 1(TD1) was present in 14.5% of patients compared to a prevalence of 0.08 to 0.24% in similar age ranges. This was partly due to the fact that all TD1 patients were routinely screened for CD. All children with T1D, abnormal anti-tTG IgA underwent esophagogastroduodenal endoscopy with Marsh classification consistent with CD. The percentage of biopsies with a Marsh score greater than IIIB was 42%, whereas 3 (4.8%) patients were also diagnosed with eosinophilic esophagitis (EoE). Moreover, 40% of our patients diagnosed with CD were referred from pediatric endocrinologists.

Conclusion: Our findings confirm the strong association between CD and endocrine autoimmunity. The systematic screening for CD in T1D and autoimmune thyroiditis is useful and clearly indicated. Conversely, there is no indication for systematic screening for endocrine autoimmunity in CD patients until effective preventive strategies for them are available

P2-215**Intestinal ganglioneuromatosis as first manifestation of multiple endocrine neoplasia 2B in a premature girl**

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Introduction: Multiple endocrine neoplasia 2B (MEN2B) is a rare cancer syndrome primarily caused by the M918T (95%) and A883F (<5%) germline mutations in the *REarranged during Transfection (RET)* proto-oncogene. Aggressive and early onset thyroid medullary carcinoma is the hallmark of the disease. Cure rates in M918T carriers who had thyroidectomy before and after 1 year of age were 83% and 15% respectively. More than 80% arise due to de novo mutations challenging the recommendation of thyroidectomy before 1 year of age as extra-endocrine features are subtle in infancy.

Case: We report a girl born by spontaneous vaginal delivery at gestational age 24 + 6 weeks who was unwell with aspirates, abdominal distention and constipation from day 1. Passing of meconium did not occur until day 3 of life. At age 3 weeks abdominal symptoms worsened with increasing amounts of green aspirates and lactate rise. Necrotizing enterocolitis (NEC) was suspected. A laparotomy confirmed chronic paralytic ileus in accordance with dilated bowels on previous abdominal films, and without NEC, malrotation or stenosis. In spite of motility stimulating drugs and rectal washouts, symptoms did not improve, and the girl was failing to thrive. At age 10 weeks she was given an ileostomy to deflate the bowels and alleviate secondary compromised breathing. Proximal to the stoma the bowels were noted to be extremely dilated as opposed to distally where they were collapsed. The pathology report from a specimen of excised bowel described intestinal ganglioneuromatosis. At age 12 weeks genetic analysis confirmed the RETM918T germline mutation aided by the history as the mother had informed, she carried this mutation.

Discussion: Dysmotility in MEN2B is due to abnormal proliferation of intramural ganglion cells resembling symptoms of Hirschsprung's disease. Gastrointestinal problems with severe constipation and pseudo obstruction are common (65%) in MEN2B and may present already in premature neonates. With increasing age marfanoid body proportions, mucosal neuromas, alacrima, corneal hypertrophy and musculoskeletal symptoms start to present.

Conclusion: Awareness and identification of extra-endocrine features occurring in early life for clinicians to suspect MEN2B is paramount for early diagnosis and timely prophylactic thyroidectomy.

P2-216

Hypothyroidism in a two and a half year-old boy with an Angelman Syndrome (AS)

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Introduction: Angelman syndrome is caused by de novo maternal deletions in 15q11-q13 region of chromosome 15 in approximately 70% of affected children.

Patient and Methods: A two and a half year-old boy with hypotonia, absence of speech, low weight (-4.38 SDS) and short stature (-1.14 SDS) had pale skin and typical facial features with wide and prominent forehead, low-lying ears, wide mouth, small and widely spaced teeth. The boy was born small for gestational age (SGA) with birth weight (-2.0 SDS) and birth length (-1.09 SDS) in 39th gestational week (GW). He had an early onset of seizures treated and controlled by antiepileptic drugs.

Results: The IGF1, IGF BP3, thyroxine (T4) and anti-thyroid peroxidase antibody (anti TPO) serum concentrations were within reference range, but thyroid stimulating hormone (TSH- 14.5uIU/ml) level was elevated for his age and sex. Karyotype was 46, XY. An EEG revealed right-sided focus of slow waves. Multiplex ligation probe amplification (MLPA) and a methylation analysis (MS-MLPA) detected a deletion in 15q11-q13 region of chromosome 15 with minimal length of 3Mb and an absence of maternal allele. His TSH (7.3uIU/ml) serum concentration decreased and he grew by 3cm after two months of replacement treatment with Levothyroxine.

Conclusions: This is a description of two and a half year-old SGA born boy with two very rare associated conditions, an Angelman syndrome and hypothyroidism. The molecular analyses confirmed maternal origin of deletion in the critical region of chromosome 15.

Key words: an Angelman syndrome, hypothyroidism, small for gestational age, MS-MLPA

Pituitary, Neuroendocrinology and Puberty

P2-217

Effect of testosterone enanthate therapy on adult height, genital maturation, and bone mineral density in children and adolescents with male hypogonadotropic hypogonadism

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Background: Testosterone enanthate (TE) therapy was established for children and adolescents with male hypogonadotropic hypogonadism (c/a MHH). However, the effect of TE therapy on adult height (AH), genital maturation, and bone mineral density (BMD) in c/a MHH has not been described well.

Objective: To assess the effect of TE therapy in c/a MHH on the achievement of genetic height potential, pubertal development, and bone acquisition and the possible adverse effect on spermatogenesis by subsequent gonadotropin therapy.

Methods: This study retrospectively evaluated c/a MHH patients who were treated with TE at Department of Pediatrics at Keio University Hospital between April 1984 and March 2019. We excluded patients with history of gonadotropin therapy before TE therapy or those with *NR0B1* mutation. We reviewed medical records and analyzed variables included AH, target range (TR), pubic hair Tanner stage, stretched penile length (SPL), and lumbar BMD by DXA before TE therapy and after the attainment of AH, as well as sperm concentration by subsequent gonadotropin therapy.

Results: The present study included 18 c/a MHH, six of whom had isolated hypogonadotropic hypogonadism, five had idiopathic hypopituitarism, four had hypopituitarism due to brain tumors, and three had Kallmann syndrome. The median age at the start of TE therapy was 15.1 (range: 13.3 – 22.9) years. The median age at the attainment of AH was 18.9 (range: 17.1 – 24.8) years. The median duration of TE therapy until the attainment of AH was 3.7 (range: 1.8 – 6.3) years. The median AH (N=18) was 175.5 (range: 160.1 – 187.6) cm. All of AH were greater than the lower limit of TR. Pubic hair Tanner stage (N=16) remained 1 or 2 before treatment, reached 4 or 5 after the attainment of AH. The median of SPL Z-score (N=17) was -3.1 (range: -7.3 – -1.4) before treatment and -1.4 (range: -3.5 – -1.7) after the attainment of AH ($P=0.004$). The median of lumbar BMD Z-score (N=15) was -3.5 (range: -4.8 – -0.9) before treatment and -2.4 (range: -3.2 – -0.00) after the attainment of AH ($P=0.005$). Five of seven (71.4%) patients achieved sperm concentration of $\geq 1.5 \times 10^6 / mL$. A patient with azoospermia had untreated bilateral cryptorchidism at 22 years old.

Conclusion: These data indicate that TE therapy in c/a MHH is effective in achievement of appropriate AH for genetic potential, maturation of external genitalia, and improvement of BMD and also suggest that subsequent gonadotropin therapy can induce spermatogenesis.

P2-218**The difference of body mass index (BMI) score before and after gonadotropin-releasing hormone agonist (GnRHa) treatment in central precocious puberty girls**

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Purpose: We investigated the difference of body mass index (BMI) score before and after gonadotropin-releasing hormone agonist (GnRHa) treatment in central precocious puberty girls (CPP).

Methods: Medical records of 188 girls with CPP treated with GnRHa were reviewed. All patients completed the therapy. The patients were categorized into two groups according to initial BMI; normal weight group (BMI < 85 percentile) and overweight/obesity group (BMI ≥ 85 percentile). We analyzed chronologic age (CA), bone age (BA), BA advancement (BA-CA), height (Ht), Ht-standard deviation score (Ht SDS), BMI, BMI SDS, predicted adult height (PAH) before treatment initiation and after treatment completion.

Results: Initial BA, Ht SDS, PAH, mid-parental height and the total durations of treatment showed no differences between two groups. But initial CA of the overweight/obesity group was lower than that of normal group and BA-CA of the overweight/obesity group was higher than that of the normal group. When comparing the height outcomes of two groups, ΔPAH showed no differences between two groups. BMI SDS increased only in the normal weight group. On multiple regression analysis, ΔBMI SDS was negatively correlated with initial BMI SDS ($r = -0.32, P < 0.001$), and it showed no correlation with CA, BA, BA-CA, height SDS. When the group of patients with increased BMI after the therapy was compared with the group of decreased BMI, no difference in ΔBA-CA and ΔPAH was found.

Conclusion: BMI SDS increased after GnRHa treatment in idiopathic central precocious puberty and early puberty girl whose initial BMI SDS was normal. The lower the pre-treatment BMI SDS, the more the post-treatment BMI SDS increased

P2-219**Aromatase inhibitor treatment in patient with beta-human chorionic gonadotrophin secreting tumor and gonadotropin-independent precocious puberty**

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Introduction: CNS tumors may cause precocious puberty (PP); in most cases gonadotropin-dependent PP, but in boys β-HCG-secreting tumors may cause gonadotropin-independent (GIPP)

with extremely high testosterone secretion due to Leidig cell stimulation by β-HCG. Rapid bone maturation in such cases can lead to growth plate closure and poor final height prognosis. Aromatase inhibitor (AI) are administered in children with McCune-Olbricht disease, familial male-limited PP, and idiopathic short stature, but there is no data in children with β-HCG-secreting tumors.

Clinical Case: 6-year boy presented with signs of PP (axillary and pubic hair growth, penis enlargement, voice deepening and acne). His sexual development was at Tanner stage IV, and his testes were about 3 ml. His height was 134.2 (+2.63 SDS), weight 36.7 kg (+2.03 SDS BMI) and his bone age was 9 years. Examination revealed high testosterone 55.5 nmol/L (N<0.5), estradiol 440 pmol/L (N<69) and β-HCG 1,849.9 IU/l (N < 2.0) levels, but LH and FSH <0.1 IU/l. A brain MRI showed pineal gland tumor 38x38x32 mm. The patient was referred to treatment with carboplatin, etoposide and ifosfamide according to the SIOP CNS GCT II trial. After 1st chemo block (38 days after primary investigation) β-HCG level dropped to 106.8 mU/l, but testosterone was still elevated (51.8 nmol/L) and estradiol too (709 pmol/L), bone age progressed from 9 to 13 years. Due to rapid bone age progression, AI therapy (Exemestane 25 mg daily) was started. After 4 week treatment estradiol and testosterone level dropped to 78 pmol/L and 0.0 nmol/L, respectively. After 3rd chemo block (70 days after primary investigation) β-HCG dropped to 1.2 IU/l, testosterone to 0 nmol/L, and estradiol to 49 pmol/L. Bone age was still 13.5 years. There were no adverse events during AI treatment.

Conclusion: To our knowledge, it is the first case of AI administration in patients with GIPP due to β-HCG-secreting tumors. In this clinical case treatment was effective and safe.

P2-220**Normalized pubertal tempo of maturation and pubertal height gain in girls with MPHD, using a physiological treatment approach with natural estrogens & rhGH**

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Background: Pubertal tempo of breast development on natural sex-steroid replacement therapy in girls with multiple pituitary hormone deficiencies (MPHD) and pubertal growth spurts on adequate GH-treatment regimens were unknown in 1989 and are still not known.

Objective and Hypotheses: A hypothesis driven prototype trial^{1,2} was initiated in the late 80ies aiming to mimic normal puberty regarding both pubertal maturation (degree and tempo of breast development) and growth (pubertal height gain and adult height). For the first time, a more physiological substitution with transdermal 17β-estradiol was used together with rhGH-doses of ≥33ug/kg/day.

Study Design: Approved by Swedish Ethical Committees, MPHD girls received transdermal 17 β -estradiol treatment, within a randomised national trial on rhGH-doses during puberty (TRN number 88-177).

Six girls with at least one prepubertal year on rhGH treatment dose 33 μ g/kg/day were randomized to rhGH 33 or 67 μ g/kg/day during puberty (Genotropin®, Kabi/Pharmacia/Pfizer). Sex-steroid replacement was 17 β -estradiol patches in slowly increasing doses (5,10,12.5,25,50 μ g/day) mimicking the spontaneous pubertal tempo³. For this purpose, pharmaceutical estradiol patches (Estraderm®, Ciba-Geigy) were produced and donated.

Methods: Breast development was assessed according to Tanner³ (stage 1-5).

Height outcome: Adult height_{SDS} (AH_{SDS}) vs total height references. Pubertal height gain was estimated as change from height_{SDS} at start of 17 β -estradiol-replacement (calculated vs prepubertal height reference) to AH. Results are given as median (range).

Results: The MPHD girls had a history of oncology treatment (n =3) and craniopharyngiomas (n=3). Age at start of 17 β -estradiol replacement was median 13.1yrs (range 12.6-14.1).

Breast development: Time from start of 17 β -estradiol patch treatment (B1) until B2 was 0.3yrs (0.2 to 0.4); B2-B3 1.2yrs (0.8-1.7); B3-B4 1.7yrs (0.5-2.4); B4-B5 1.5yrs (1.0-3.1). Time for B2-B4 was 3.0yrs (1.7-4.2). The start of estradiol treatment was 2yrs late, and the tempo of median breast maturation became 1yr prolonged, compared to published³ normal ranges.

Pubertal Height Gain: Total pubertal gain in height_{SDS} was +0.8 (0-1.15); expressed in cm 21.1 (11.8-21.6). AH_{SDS} was 0.075 (-1.33 to 0.31); expressed in cm 168.0 (159.5-169.5).

Conclusion: This hypothesis driven prototype trial initiated in 1989, show for the first time that it is possible to normalize puberty in MPHD girls, both regarding the tempo of maturation of breast development, and to achieve a normal pubertal growth spurt and AH by using a more physiological substitution therapy with transdermal 17 β -estradiol and adequate rhGH-doses. This allows earlier age for pubertal induction.

^{1,2}Albertsson-Wiklund et al, Acta.Pead.1999;88(suppl):80-84;Horm.Res.Ped.2014;82:158-170.

³Marshall&Tanner, Arch.Dis.Child.1969;44:291-303.

called combined pituitary hormone deficiency (CPHD). The most common congenital CPHD is caused by mutations in genes: PROP1, POU1F1, HESX1, LHX3, LHX4, OTX2, GLI2, and SOX3. POU1F1 mutations are extremely rare among the Indo-European ethnic type (1% of all cases of congenital hypopituitarism) and more common among the Turkic peoples (7.3%, according to Turkish researchers). Due to the migration and the influx of Azerbaijanis in particular, we can observe such cases more often in St. Petersburg in recent years.

Methods: 3 Azerbaijani boys (one of them born to consanguineous marriage) were examined using standard clinical and laboratory methods. The levels of blood glucose, TSH, free T4, GH, IGF-1, ACTH, cortisol, prolactin and liver function tests were evaluated. PROP1, POU1F1, HESX1, LHX3, LHX4, OTX2, GLI2, SOX3, ARNT2, GH1, GHRH, GHRHR, GHSR, IGSF1, PAX6, SHH gene mutations were investigated by a new generation sequencing (NGS) method.

Results: Patient №1 on the second day of life had persistent hypoglycemia, accompanied by convulsions. The patient had a craniofacial anomaly, shortening of the proximal extremities. By 1 month of life he had no growth increments. Patients №2 and №3 were hospitalized at the age of 1 month due to prolonged jaundice. Patients had general symptoms of hypothyroidism, craniofacial dysmorphisms. Unconjugated hyperbilirubinemia, hypoglycemia were diagnosed. After 1 month of life they had poor growth. The diagnosis of congenital hypopituitarism was completed with confirmation of FT4, GH, PRL deficiencies. Patients 2 and 3 had severe hypothyroidism while the patient №1 had moderate hypothyroxinemia. Homozygous mutations in POU1F1 were found in all infants: missense mutation s.793S>T; p.R265W (patient №1) is pathogenic and early described; frameshift mutations s.638_642delGGAAAP. R212KfsX12 (patient №2) and c.634_638delGAAAGp.R213KfsX12 (patient №3). In the latter two cases mutations were not previously considered to be pathogenic. Replacement therapy with levothyroxine and then growth hormone led to the elimination of hyperbilirubinemia, hypoglycemia.

Conclusion: Infant jaundice and /or persistent hypoglycemia require CPHD exclusion, moreover male gender and Turkic ethnic type increase the risk of the POU1F1 mutation. Thyrotroph dysfunction degree determines the severity of clinical and laboratory manifestations of the hypothyroidism syndrome and can be associated with the type of genetic defect.

P2-221

The case of congenital hypopituitarism due to mutation POU1F1 in 3 Azerbaijani newborn boys

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Background: Growth hormone deficiency in conjunction with the function loss of other anterior pituitary hormones is

P2-222

Case report of syndrome of inappropriate antidiuretic hormone secretion (SIADH) caused by rare AVPR2 gene active mutation

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Objective: The AVPR2 gene mutation usually cause nephrogenic diabetes insipidus. We report a patient who carried an active gene mutation of AVPR2 presenting persistent hyponatremia,

which resembled to the syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Method: We describe a patient whose clinical and laboratory evaluation were consistent with hyponatremia, which hardly to be corrected to normal. After the AVPR2 gene mutation identified, the level of serum sodium was increased with furosemide orally.

Result: The patient was 5 years old boy with several times generalized seizures caused by hyponatremia in 2 years. His sister was in good health. There was no family history of hyponatremia. He showed apathy with otherwise normal physical examinations. His blood pressure was normal, his height and weight were in normal range. Initial laboratory evaluations demonstrated hyponatremia of 120 mmol/L with inappropriately elevated urinary sodium levels of 181.7 mmol/L, and the serum levels of potassium and bicarbonate were normal. The serum osmolality was lower to 252 mOsm/L. He had normal blood urea nitrogen and low serum creatinine levels. Adrenal hormone and thyroid-function tests were all normal. Imaging studies of the head and chest were unremarkable. Despite clinical and laboratory presentations consistent with the presence of SIADH, we cannot find any pathogenic reasons. The hyponatremia was hardly to be corrected by high doses of sodium supplementation.

DNA sequencing of the patient's AVPR2 gene identified missense mutations of nucleotide 770 mutated from cytosine to thymine, which changed codon 137 from arginine to cysteine. This mutation was reported as constitutive activation of AVP receptor by other researchers.

The patient was initially treated with fluid restriction and high doses of sodium supplementation, but both were useless. He was treated with furosemide, resulting in increased urinary output and normalization of the serum sodium level.

Conclusion: The gene mutation can cause nephrogenic diabetes insipidus and SIADH, depending on the kinds of mutations. The administration of furosemide normalized the serum sodium level and increased the urinary output. The AVP antagonist of Tolvaptan could suppress AVP receptor activity, which could prescribe to SIADH, but is more expensive than furosemide.

P2-223

Long term effects of GnRH agonist therapy on BMI in girls with idiopathic central precocious puberty

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Background: Studies investigating effects of GnRHa therapy on body weight (BW) and BMI in subjects with CPP are generally including short term effects.

Aim: To investigate changes in BMI at the beginning, during and two years after completion of GnRHa therapy to determine influential factors in girls with idiopathic CPP.

Methods: Data of 138 girls who completed GnRHa therapy for iCPP were evaluated retrospectively. All of subjects underwent weight and height measurements at beginning and end of therapy, and 111 of the study population underwent weight and

height measurements two years after completion of therapy. CDC percentile curves were used for BMI assessment.

Results: Mean age of subjects at beginning of therapy was 8.5 ± 1.0 yrs, mean bone age was 10.7 ± 0.9 yrs and duration of therapy was 29.9 ± 9.2 months. At beginning of therapy, 82(59.4%) had normal BW, 42(30.4%) were overweight, and 14(10.2%) were obese. By end of therapy, 12.2%(10/82) of subjects with normal BW had become overweight, and 2.4%(1/42) of overweight had become obese; while 92.9%(39/42) of overweight and 78.6%(11/14) of obese subjects maintained their weight. BMI-SDSs of subjects at beginning, end and two years after completion of therapy are presented in Table 1. Multivariate regression analysis revealed that among factors affecting BMI-SDS change(Δ BMI-SDS) such as age, initial BMI-SDS and duration of therapy, most significant was initial BMI-SDS, which had negative correlation with Δ BMI-SDS($r^2:0.34, p:<0.001$).

Conclusion: Present study is one of the unique studies evaluating BMI change over a long term of period. Although BMI-SDS increased during GnRHa therapy in normal weight girls, it was reversible in long term follow-up after therapy. However BMI-SDS did not change during and in long term follow-up after GnRHa therapy in overweight and obese girls. Conserving BMI-SDS in overweight or obese subjects during therapy may be related to the fact that BW management programs were generally recommended and applied on these subjects. Dietary recommendations should be provided for children with normal BW who undergo GnRHa therapy for CPP, as is the case for overweight patients.

Table 1. Changes in BMI-SDS during and after GnRHa therapy

	All Cases (n: 138)	Normal-Weight (n: 82)	Overweight/ Obese (n: 56)
At the beginning of therapy	0.92 ± 0.74	0.42 ± 0.54	1.66 ± 0.48
At the end of therapy	1.20 ± 0.51	0.87 ± 0.33	1.69 ± 0.53
Two years after therapy	0.90 ± 0.62	0.40 ± 0.48	1.65 ± 0.52
P value	<0.001	<0.001	0.205

P2-224

To whom should central nervous system imaging be performed in girls with central precocious puberty (CPP)?

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Background: Organic lesions are present in 5-10% of cases with CPP. Determinants of an increased risk for organic pathology underlying CPP in girls are debatable. CNS imaging is recommended for girls who have pubertal signs before 6 years of age. Although neurological findings may suggest organic pathology, other clinical features and hormonal variables have not been adequately examined.

Aim: To analyze clinical&hormonal characteristics that would point to an organic pathology, thus requirement of CNS imaging in girls with CPP.

Methods: Medical records of 286 girls who had GnRHa therapy for CPP were evaluated retrospectively. All cases had CNS imaging either cranial or pituitary MRI. Chronological age, bone age, height, pubertal stage, gonadotropin and serum estradiol levels, peak stimulated LH level as well as findings of CNS imaging at time of diagnosis were evaluated. Cases with CNS pathology on MRI were classified as organic CPP. Parameters that differentiate organic from idiopathic CPP(iCPP) were determined using ROC curves.

Results: Organic CPP was detected in 6.3%(18/286) of cases. Girls with organic CPP were diagnosed at an earlier age, bone ages were more advanced, bone age-corrected height-SDSs were lower and sex steroid levels and peak stimulated LH levels were higher than girls with iCPP. Puberty started before 6 years of age in 88.9%(16/18) of girls with organic CPP. Mean basal estradiol and peak LH levels of patients with organic CPP at any pubertal stage were similar to those of iCPP at advanced pubertal stages such as Tanner 4(for estradiol 65.2 ± 22.4 vs 64.6 ± 21.2 pg/ml, for peak stimulated LH 16.6 ± 5.8 vs 17.2 ± 3.6 IU/L,respectively). Basal estradiol and peak stimulated LH levels were higher in organic CPP than idiopathic cases with matched pubertal stages. Threshold values to distinguish organic and iCPP at Tanner stages 2&3 were 38.1pg/ml for basal estradiol (100%sensitivity,80.4%specificity), and 13.6IU/L for peak LH (100%sensitivity,66.4%specificity).

Conclusion: Pubertal symptoms and signs generally begin before 6 years of age in organic CPP in girls.Hormone levels are much higher than expected according to stage of puberty. CNS imaging is suggested for girls younger than 6 years of age since risk of detecting an organic pathology is higher in this age group. High levels of gonadotropins and sex steroids discordant with stage of puberty may be another indication for imaging regardless of age. CNS imaging should be prioritized in those with an estradiol above 35pg/ml and/or a peak LH above 10IU/L in early stages of puberty(T2&3).

P2-225

Unusual presentation of McCune-Albright syndrome in a 10-year-old girl

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Case Report: A 10-year-old Italian girl presented with a painless, hard swelling in left fronto-orbital region noted two years earlier. She had no headache or other symptoms; ophthalmologic evaluation revealed no signs of intracranial hypertension; the visual field showed a reduced level of sensitivity in the upper sector of the left eye. Her previous medical history was not relevant except for a mild head injury reported two years earlier. The girl was a second born after an uneventful pregnancy with normal delivery from unrelated parents without significant illnesses. Birth weight was 3700 g, psychomotor development had been regular and no previous hospital admissions were reported. At clinical examination, the child was in good general condition. Neurologic examination was unremarkable. Her Tanner stage was B1PH3. She did not show café-au-lait spots. The weight was 52.5 kg (+1.68 SDS), height 161.5 cm (+3.2 SDS) and BMI 20.1 kg/m² (+0.64 SDS). A brain CT and MRI showed an fibro-osseous lesion of the cranial base, extending to the orbit and left frontal region with obliteration of the left frontal and sphenoid sinuses and partial obliteration of the ethmoid sinus. The pituitary appeared enlarged with a convex upper margin and two small areas of altered signal of the parenchyma with delayed gadolinium uptake (3 and 5 mm in diameter). The remaining radiograph of the skeleton showed no lesions. Endocrine examination showed high IGF-1 (908 ng/ml,n.v.123-427) and high basal GH levels (36 ng/ml,n.v.<8.05) that resulted not suppressed during oral glucose toleration test (nadir GH 29.1 ng/ml). A hyperprolactinemia was also revealed (451 ng/ml, n.v.4.8-23.3); levels of IGFBP3, TSH,FT4, ACTH, cortisol, blood glucose and electrolytes resulted normal. FSH, LH and 17-beta-estradiol resulted in pre-pubertal ranges. Pelvic ultrasound showed a pre-pubertal appearance of uterus and ovaries without ovarian cysts. A neurosurgical treatment was programmed; the genetic investigation for McCune-Albright syndrome (MAS) is ongoing.

Discussion: MAS, a complex disorder due to postzygotic somatic activating mutations in GNAS1 gene, is characterized by fibrous dysplasia (98% of patients in a large cohort) (Collins et al, 2012), café-au-lait spots (66%) and hyperfunctioning endocrinopathies. The latter are mainly represented by precocious puberty (50%), more rarely by hyperthyroidism (28%), renal phosphate wasting (43%), growth hormone (GH) and/or prolactin hypersecretion (21%) and hypercortisolism (4%) (Yao et al, 2017). GH excess represents a serious complication and it is almost always associated with skull base fibrous dysplasia (Salenave et al, 2014). Cases of patients treated conservatively are reported in literature (Classen et al, 2012).

P2-226**Endocrine transition of care from pediatric to adult medicine in adolescents and young adult survivors of childhood brain tumour. Experience at Hôpital Universitaire Necker-Enfants Malades and Hôpital Universitaire La Pitié-Salpêtrière – A follow-up study of the 2010-2015 cohort**

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Background: Childhood brain tumour survivors are at risk of developing endocrine secondary effects throughout lifetime. Transition between childhood and adult care is a critical moment during which patients may stop medical visits and treatments.

Objective: To describe endocrine care transition in our cohort of patients with primary brain tumors followed from 2010-2015, who are ≥18 years old by December 31st 2017.

Methods: Retrospective and prospective observational study, data collection from medical records of patients seen at least once between 2010-2015. Patients with pituitary adenomas, untreated fortuitously diagnosed gliomas (NF1 context), who died before transition or with insufficient data were excluded.

Results: 74 patients were included (34 females), with a mean age of 21.7 years (17.1-29.9). Tumour types: medulloblastomas (37.8%), craniopharyngiomas (36.5%), gliomas (13.5%), dysgerminomas

(5.4%), others (6.8%). Fifty-nine out of 74 (79.7%) have started transition, 9 (12.2%) are still in regular pediatric care; 2 have been considered as not needing adult endocrine follow-up, and 4 are lost to follow-up before starting transition. Forty-four out of 59 who started transition (74.5%) have been seen at La Pitié-Salpêtrière hospital or other adult centres in the last year.

Endocrine deficiencies: growth hormone deficiency (GHD): 89.2%, 57/66 diagnosed during childhood (43/57 within the first year of endocrine follow-up) and 9/66 after attaining adult height. At transition reevaluation, 60/66 have persistent GHD and 4/66 have a normal GH response ($\geq 15 \text{ mUI/L}$). TSHD or peripheral hypothyroidism concerns 71.6% of patients. Routine thyroid ultrasound was performed in 28 patients; 15 of them have thyroid nodules, including two cancers (5.5 and 11 years post radiotherapy). ACTHD affects 51.3% patients. Hypogonadotropic hypogonadism affects 43.2% patients, and gonadal insufficiency, 24.3%. Diabetes insipidus affects only suprasellar tumors (28/39). Mean final height is lower in patients with non suprasellar tumors: $-0.8 \pm 1.3 \text{ SD}$ compared to suprasellar: $0.1 \pm 1.4 \text{ (p=0.01)}$, attributable to spinal radiotherapy. BMI is higher in patients with suprasellar tumors: $29.2 \pm 9.2 \text{ Kg/m}^2$ (21% overweight, 39% obesity) than in non suprasellar: $22.6 \pm 3.9 \text{ Kg/m}^2$ (14% overweight, 3% obesity), $p < 0.001$. 27/57 reports a handicap (visual or neurological) that impairs their studies or work.

Conclusions: Transition is a critical time for patients with chronic diseases, including childhood brain tumor survivors. It is important to ensure an effective passage towards adult endocrine care, in order to maintain care continuity and prevent complications linked to non compliance to treatment. Our transition program between a pediatric and an adult hospital seems to contribute to this care continuum.

P2-227**Screening of Central Precocious Puberty (CPP) in females: efficacy of morning unstimulated luteinizing hormone (mLH) levels**

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Introduction: The gonadotropin releasing hormone stimulation test (GnRHST) is commonly used to screen CPP. Some recent studies reported that morning unstimulated luteinizing hormone levels may be sufficient to discriminate pubertal from prepubertal children. The aim of this study is to evaluate the clinical efficacy of mLH to screen CPP in females

Patients and Methods: We retrospectively studied the clinical and hormonal data of 166 consecutive girls with precocious thelarche (<8 years of age) evaluated from 2017 to 2018 at our Centre. The patients were subdivided in two groups (pubertal and prepubertal) according to the results of a standard GnRHST (LH peak $> 5 \text{ IU/L}$). BMI was calculated, normalized for Italian reference standards and reported in SDS. Bone age was assessed by Greulich-Pyle method. The sensitivity and specificity of two mLH thresholds (0.3 IU/L and 0.2 IU/L) to screen CPP in females were evaluated.

Results: 61 pts were pubertal and 105 were prepubertal. Between the 2 groups, chronological age (7.94 ± 1.02 vs 7.62 ± 1.16), bone age for chronological age (1.78 ± 0.99 vs 1.24 ± 1.44) BMI SDS (-0.02 ± 0.85 vs 0.26 ± 1.12) at diagnosis did not show any differences. mLH (1.26 ± 1.24 vs 0.21 ± 0.23), mFSH (4.74 ± 2.05 vs 2.47 ± 1.5) and the mLH/mFSH ratio (0.25 ± 0.23 vs 0.1 ± 0.1) are significantly higher in pubertal girls ($p < 0.001$). A linear significant ($p < 0.001$) correlation between LH peak at 30' and mLH (R: 0.73), mFSH (R: 0.64), mLH/mFSH (R: 0.42) ratio was found. In our patients, the sensitivity of a mLH threshold ≥ 0.3 IU/L to identify CPP is 80% and the specificity was 76%; a lower threshold (≥ 0.2 IU/L) increased the sensibility (95%) but dramatically reduced the specificity (60%).

Conclusion: Our data seem to confirm the correlation between mLH and LH peak after GnRHST in pubertal girls. mLH levels ≥ 0.3 IU/L should be cautiously considered sufficient to screen CPP in females, but larger data are mandatory to confirm our results.

P2-228

Near adult height according to genetic target and absence of craniofacial bone fibrous dysplasia in a girl with mc cune albright syndrome and growth hormone excess: 12.6 Years follow-up

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Background: Mc Cune Albright (MAS), is a rare genetic disease clinically defined by bone fibrous dysplasia (BFD), café au lait skin spots and at least one hyperfunction endocrinopathy. Growth Hormone (GH) excess has been described in 20% of patients usually accompanied by hyperprolactinemia (80%). As reported in literature GH hypersecretion is always associated with craniofacial BFD, macrocephaly and is also accompanied by higher risk of systemic morbidity. Medical therapy is first line treatment and includes somatostatin analogs, GH receptor antagonist, and dopamine agonists. Treatment goal is to maintain IGF1 Z-score between -2 + 1 SDS and growth velocity according to Tanner stage, sex and age.

Aim: We report a long term outcome on somatostatin analogue and cabergoline treatment for growth hormone excess in a girl with MAS.

Clinical Case: A 15 year old girl, without personal and family relevant history, was sent for endocrinological evaluation at 2.72 years, because of tall stature (height +2.57 SDS), high growth velocity (12cm/y) and advanced bone age (4y). Physical exam showed no pubertal signs and a large café au lait skin spot characteristic of MAS. GH excess was diagnosed by a paradoxical response on OGTT (GH 13.4ng/ml) and high IGF1 Z-score (+ 3.32 SDS). No other endocrinopathies were detected. Pituitary MRI was normal. Octreotide LAR was started at 0.15mg/kg every 28 days. After 1 year follow-up cabergoline was added at 1mg/week, due to the lack of full response on auxiological (growth velocity 9cm/y) and analytical parameters (IGF1 Z-score +1.25 SDS; GH 5ng/ml; PRL 39pg/ml). Under combined treatment all parameters normalized,

and remained according to sex, age and Tanner stage. Menarche was presented at normal age (12.56 y). She reached near adult height (169.3cm) according to genetic target (169.9cm) with a height growth velocity of 1.7 cm/y. During 12.6 years of follow-up, no other endocrinopathies were diagnosed, pituitary MRI remained normal and no adverse events appeared. Craniofacial BFD and long BFD were not found neither in current head CT nor in 99mTC MDP bone Scintigraphy.

Conclusions: To our knowledge this is the youngest patient treated with somatostatin analogue and cabergoline. Our data suggest that early treatment with strict compliance could prevent craniofacial complications. This clinical case emphasizes the effectiveness and safety of an early combined treatment in a girl with MAS and GH excess. Further studies with greater number of patients are needed to confirm these conclusions.

P2-229

Normalized pubertal tempo of masculinisation and pubertal height gain in boys with MPHD, using a physiological treatment approach with low dose testosterone and adequate dose rhGH

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Background: Masculinisation tempo on sex-steroid replacement in boys with multiple pituitary hormone deficiencies (MPHD) and pubertal growth spurts on adequate GH-treatment regimens were unknown in 1989 and are still not optimal.

Objective and Hypotheses: A hypothesis driven prototype trial^{1,2} was initiated in the late 80ies aiming to mimic normal puberty³ regarding both degree and tempo of masculinisation and pubertal height gain and adult height (AH). For the first time, low testosterone doses were used together with rhGH-doses of $\geq 33\text{ }\mu\text{g}/\text{kg/day}$.

Study Design: Approved by Swedish Ethical Committees, testosterone-treatment was given to MPHD boys, a subgroup in a randomised national trial on rhGH-doses during puberty (TRN 88-177).

10 boys with \geq one prepubertal year on rhGH treatment $33\text{ }\mu\text{g}/\text{kg/day}$ were randomized to rhGH $33/67\text{ }\mu\text{g}/\text{kg/day}$ during puberty (Genotropin®, Kabi/Pharmacia/Pfizer). Sex-steroid replacement was oral testosterone undecanoate (Undestor®, Organon), in increasing doses (10, 20, 40mg/d) followed by parenteral Testoviron depot®, (Schering).

Methods: Genital development was assessed according to Tanner³ (stage 1-5).

Height outcome: AH_{SDS} vs total height reference. Pubertal height gain was estimated as change (Δ) from height_{SDS} at start of testosterone replacement (vs prepubertal height reference) to AH. Results are given as median (range).

Results: The MPHD boys had a history of oncology treatment (n = 3) or congenital anomaly (n=7). Age at start of testosterone replacement was median 13.8yrs (range 11.8 to 15.8).

Genitalia development: Time from start of testosterone (G1) until G2 was 1.1yrs (0.3-3.0); G2-G3 1.2yrs (0.6-2.1); G3-G4 1.2yrs (0.3-2.3); puberty time G2-G4 2.5yrs (1.7-3.2); G1-Gmax 4.8yrs (2.2-5.8). Age at treatment start was late, but the masculinization tempo G1-G3 became within published³ normal ranges. 8/10 needed parenteral testosterone for progress from G3 to G4/5.

Height outcome: Total pubertal gain in height_{SDS} was +0.58 (-0.51 to 2.33); expressed in cm 32.0 (19.7-37.2). AH_{SDS} was 0.36 (-0.34 to 1.38); expressed in cm 182.8 (178.2-189.5).

According to GH doses: GH³³ ΔH_{SDS} 0.24 (-0.51 to 0.58), GH⁶⁷ ΔH_{SDS} 1.8 (-0.29 to 2.33).

Conclusion: This hypothesis driven prototype trial initiated in 1989, show for the first time that it is possible to normalize puberty in boys with MPHD, both regarding tempo of genitalia development, pubertal growth spurt and AH using a low dose therapy with testosterone and adequate rhGH doses. Induction with oral testosterone dose was favourable for genital development and growth, but was insufficient for complete maturation. These positive results will allow puberty induction in MPHD boys at normal age.

^{1,2}Albertsson-Wikland et al, Acta Paed. 1999;88(suppl):80-84; & Horm. Res. Ped. 2014; 82:158-170.

³Marshall & Tanner, Arch. Dis. Child. 1970;45:13-21.

gravity was significantly lower in CDI than in PP (1.005±0.002 vs. 1.015±0.004, P=0.004). The amount of drinking and urine volume was significantly higher in CDI than in PP (3618±850 vs. 1900±529 ml/m², P=0.0006, 3707±1278 vs. 13641±881 ml/m², P=0.001). Urine osmolality tended to be lower in CDI than in PP (135.5±35 vs. 430.4±306.6 mOsm/kg, P=0.09). MRI was performed in 5 patients of CDI and 4 patients of PP. Posterior pituitary bright spot showed absence in all 5 CDI and 1 PP patients in T1-weighted image. Pituitary gland and stalk of 4 CDI patients showed abnormal findings, such as pituitary gland enlargement and pituitary stalk thickening. Whereas, 3 PP patients showed normal MRI findings.

Conclusions: The incidence of T1DM was 2.2 per 100,000 population, and the incidence of CDI was 0.7 per 100,000 population of children. Our data suggests that the urine specific gravity, the amount of drinking and urine volume, urine osmolality and MRI may be predictive factor for differentiation between CDI and PP.

P2-231

Macroprolactinoma presenting with Pituitary Apoplexy associated with middle cerebral artery infarction in an adolescent male

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Background: Pituitary apoplexy is a clinical syndrome caused by haemorrhage of the pituitary gland, typically characterised by acute confusion, headache, vomiting and visual disturbance. It is regarded as a medical emergency. It is rare in childhood and adolescence, occurring in association with pituitary tumours. We report an unusual case of pituitary apoplexy associated with a cerebral infarction secondary to internal carotid artery compression.

Case: 16 year old male presented to Emergency Department with acute onset confusion, visual disturbance, slurred speech and right-sided weakness. There was a three day history of vomiting, and two days of worsening headache. He was unable to follow commands (GCS 11:E4V2M5). Examination revealed right-sided increased tone, reduced power and bi-temporal hemianopia.

The patient was initially managed according to "stroke" guidelines. CT head revealed 3.5x2cm sellar/suprasellar mass. Urgent endocrine profile revealed Prolactin (x20 dilution) 87089mIU/L [100-410mIU/L], Cortisol 494nmol/L [130-580nmol/L], TSH 1.0mIU/L [0.3-5.5mIU/L], T4 5.5pmol/L [9-25pmol/L]. Serum Sodium 127mmol/L and Osmolality 271mosmo/kg supported inappropriate ADH secretion. These results were consistent with diagnosis of macroprolactinoma with TSH deficiency.

CT angiography within 24 hours showed luminal occlusion of both internal carotid arteries secondary to tumour mass effect. MRI confirmed pituitary apoplexy with haemorrhagic fluid levels. Ischaemic changes were also seen in left fronto-parietal, middle cerebral artery (MCA) region.

Treatment was commenced with 100mg IV Hydrocortisone STAT on admission and subsequently 250micrograms oral Cabergoline. Within 24 hours there was improvement in focal neurology and vision. Endoscopic trans-sphenoidal debulking of

P2-230

The incidence and diagnostic factors of polydipsia and polyuria: a single center survey in Japan

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Introduction: Polydipsia and polyuria are one of the common chief complaints in the field of pediatric endocrinology. The differential diagnosis of polydipsia and polyuria are various diseases including diabetes mellitus (DM), central diabetes insipidus (CDI), and primary polydipsia (PP). Although DM is not difficult to diagnose, between DI and PP is sometimes difficult.

Aim: The objective of our study is to reveal the incidence of CDI, and to investigate predictive factors for differentiation between CDI and PP.

Methods: This study was a retrospective chart review, and performed from January 2014 to December 2018 in Department of pediatrics, Kurume University Hospital in Japan. The chief complaints of the patients, whose age was under the age of 15 years, were polydipsia and polyuria.

Results: The number of first time patients was 1611 during this period. The number having the chief complaint of polydipsia and polyuria was 27. Type 1 DM (T1DM) was found in 16 out of the 27 patients, CDI was found in 5 out of 27, PP was found in 5 out of 27, and nocturnal enuresis was found in 1 out of 27. The incidence of T1DM was 2.2 per 100,000 population, CDI was 0.7 per 100,000 population in this study. Age, sex, duration of symptoms, height SD, Na, Hb, Alb, BUN, plasma/urine osmolality, and AVP had no significant differences between CDI and PP. The urine specific

tumour was performed within 48 hours. Post-operative imaging confirmed significantly debulked sellar/suprasellar mass with a maturing left MCA infarct. Histology showed pituitary adenoma with strong immunopositivity for prolactin with increased proliferation, Ki-67 index 7%.

Maintenance Hydrocortisone, Levothyroxine and Cabergoline 250 micrograms twice weekly were commenced. Repeat Prolactin day 5 was 3491mIU/L. Cabergoline was increased to 500micrograms twice weekly and within 2 weeks Prolactin reduced to 645mIU/L. Further clinical assessment revealed delayed puberty (G3 PH2 TV5ml) consistent with longstanding hyperprolactinaemia effect. Post-operative visual fields were normal.

Neuro-rehabilitation assessments revealed significant cognitive difficulties. Prior to this event the patient was functioning at a good cognitive level according to school reports. Ongoing neuro-rehabilitation is integral to his ongoing care.

Outcome: Clinical surveillance to review evolving pituitary hormone replacement, definitive tumour management and neurological outcome are in progress.

Conclusion: Cerebral infarction following pituitary apoplexy and internal carotid artery occlusion is rare. Cranial MRI scan (to confirm pituitary apoplexy) and CT angiography helped understand the pathophysiology.

P2-232

Childhood craniopharyngioma: clinical picture at diagnosis in an Italian multicentre study

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Diagnosis of craniopharyngiomas in childhood is often delayed due to nonspecific symptoms. In Italy all children are followed-up by paediatricians of the NHS and paediatric endocrinologists are present throughout the country. This would theoretically lead to an early diagnosis. We aimed to examine the clinical picture at diagnosis and duration of history before diagnosis in 117 patients (pts) followed-up at Endocrinology Centres belonging to the I.S.P.E.D.

Methods: we retrospectively evaluated 117 pts from 14 centres, diagnosed after 01/01/2000. Auxological data, clinical presentation, duration of symptoms, tumor location (intra/suprasellar) and 3rd ventricle involvement were analyzed.

Results: Mean age at diagnosis was 8.3 yrs (0.1-18yrs, one case diagnosed prenatally) and 41% of pts were younger than 7 yrs. Median duration of symptoms was 10.2±12.4 mo. (range 0-60 mo.), and was positively correlated with age ($r=0.21$, $p=0.02$), in particular pts younger than 7 yrs had a shorter duration of symptoms (6.2 mo.± 0.9 vs 12.8 mo.± 1.8, $p < 0.03$). The most common symptom at diagnosis was headache (57%) (alone in 9.4%, associated with vomiting in 11%, visual impairment in 33% (alone in 13%, with other symptoms in 20%) followed by growth impairment in 25% (alone in 12%, associated with other symptoms in 13%). In the 14 pts > 13 yrs of age 14% had delayed puberty. Pts with symptoms related to increased intracranial pressure showed a shorter clinical history (6.1 mo.±1.2). Taken alone, headache and visual loss carried to a delayed diagnosis (12.9 mo.±4.4). Endocrine deficits were present at diagnosis in 60.2% of pts, the most frequent being GHD (64.8%), followed by TSHD 37% and ACTHD 5.5%. Patients with endocrine deficiencies had a tendentially longer duration of symptoms (11.9 mo.±1.7 vs 8.8 mo.±1.8; p ns). In 91 pts (79%) the lesion was suprasellar, in 15 pts (13.1 %) intrasellar and in 8 pts (7%) intra/suprasellar. Tumor size, location (intra/suprasellar) and 3rd ventricle involvement were not related to duration of symptoms. The suprasellar location was positively correlated with BMI-SDS ($p=0.03$).

Conclusions: Also in Italy the diagnosis of craniopharyngioma is often delayed, especially in older children. The tumor extension with hypothalamic involvement correlated with elevated BMI at diagnosis. Headache and vomiting were the symptoms leading to a prompt diagnosis in younger children, whereas puberty delay was frequent at puberty. Headache with visual deficits and growth impairment, should be considered first of all by general paediatricians as alarming symptoms.

P2-233

Abstract withdrawn

P2-234

Evaluation of Clinical Features and Treatment Responses of Cases with Hyperprolactinemia

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Aim: In this study, we planned to evaluate the patients with hyperprolactinemia etiology, clinical features and treatment responses.

Material and Method: We evaluated retrospectively the features, clinical follow-up data and treatment responses of the patients with hyperprolactinemia in our pediatric endocrinology clinic between 01.01.2012-31.12.2018.

Results: Thirty-one patients with hyperprolactinemia underwent follow-up in a seven-year period. The mean age of these cases was 15.7 ± 1.5 years. 27 cases (87.1%) were female. The most common complaints in girls were menstrual irregularity / amenorrhea ($n = 14$) and galactorrhea ($n = 8$). In terms of etiology, microadenomas were observed in 9, macroadenomas in 4, idiopathic hyperprolactinemia in 12, and drug-induced hyperprolactinemia in 4 cases. The mean prolactin level in the whole group was 104.7 ± 145.4 (27.8-813) ng/ml. According to the etiology, the mean prolactin level was 43.6 ng/ml in drug-induced hyperprolactinemia, 137.8 ng/ml in microadenomas group, 285 ng/ml in macroadenomas group, idiopathic hyperprolactinemia group was 49.6 ng/ml. All cases with a prolactin level above 100 ng/ml were diagnosed as adenoma (3 macroadenomas and 5 microadenomas). Medical treatment was performed in 24 patients (23 cases with cabergoline, 1 case with bromocriptine) and surgery was performed in 3 cases (1 patient with Rathke cleft cyst, 2 cases with macroadenomas). Seven patients were followed without treatment. Cabergoline dose was 0.52 ± 0.21 (0.25-1) mg/week, and the mean time to normalization of prolactin levels was 2.6 ± 3 (1-12) months. There were no side effects related to cabergoline. Postoperative prolactin levels did not return to normal in 2 patients with hyperprolactinemia due to macroadenomas and Rathke cleft cyst, and the need for medical treatment continued. Multiple pituitary hormone deficiencies (gonadotropin, TSH, ACTH) was diagnosed in one patient with macroadenomas. The patient's cabergoline treatment (1 mg/week) and prolactin levels returned to normal in the first month. At the eighth month, the adenomas shrank almost completely.

Conclusion: The cases diagnosed as hyperprolactinemia were mostly adolescent girls. The most common cause was the pituitary adenomas (42%) and 64% of these adenomas were microadenomas. In patients with hyperprolactinemia, a good response to medical treatment including those due to adenoma, and a small number of cases required surgical treatment.

Keywords: hyperprolactinemia, prolactinomas, cabergoline, surgery

P2-235

A Case of Gonadotropin-independent precocious puberty due to germ cell tumor in the frontal lobe

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Introduction: It is known that gonadotropin-independent or peripheral precocious puberty (PPP) may develop due to tumors that secrete beta human chorionic gonadotropin (Beta-HCG). These tumors can be located in gonads, liver, mediastinum or central nervous system. HCG-producing tumors of the central nervous system are rare, most commonly seen in the suprasellar and

pineal regions. However, any germ cell tumor (GCT) containing the syncytiotroblastic giant cell may produce HCG and potentially lead to PPP. Here, we present a male patient who was diagnosed as PPP due to GCT in the unusual location of central nervous system.

Case Report: A 9-year-old male patient was admitted to another hospital with headache, vomiting and double vision for 6 months ago. He was operated with a $7 \times 6 \times 5$ cm mass in his right frontal region. The patient underwent total excision and was diagnosed as mixed GCT on histopathological examination and admitted to our hospital for further treatment. He was consulted to the pediatric endocrinology upon detection of macrogenitalia. At the time of admission his age was 9 years and 8 months. The weight of the patient was 45 kg (+ 1.8 SDS) and 145.5 cm (+1.65 SDS). On physical examination, testicular volume was 8/8 ml, Tanner stage 4 pubic hair was observed and macrogenitalia was present (Figure 1). In laboratory evaluations, LH was 0.02 mIU/ml and FSH was <0.05 mIU/ml and total testosterone value was 839 ng/dl. Beta-HCG value in the serum and cerebrospinal fluid (CSF) were 106 IU/L (N: <5), 631 IU/L respectively. The bone age was 13 years and 6 months. Craniospinal magnetic resonance imaging (MRI) showed residual frontal mass without spinal seeding metastasis. He received chemotherapy and craniospinal irradiation. CSF and serum beta-HCG levels were normal after 3 cycles of chemotherapy. After accomplished of the treatment his LH 1.48 mIU/ml and FSH was 2.25 mIU/ml and total testosterone value was 25 ng/dl. We decided to initiate a gonadotropin releasing hormone analogue due to the fact that the bone age was too advanced.

Conclusion: Intracranial GCTs are rarely seen as a cause of PPP. Gonadotropin-independent precocious puberty due to GCT located in the frontal lobe in the brain has not been previously reported in the literature. In these patients, the bone age advance rapidly and after the oncological treatment and normalization of beta-HCG values, the hypothalamus-pituitary-gonad axis can be activated. Therefore, close follow-up is required.

P2-236

Isolated Premature Menarche into two siblings with Neurofibromatosis Type 1

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Background: Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder caused by *NF1* mutation. The condition is typified by the development of benign and malignant tumors in both the central nervous system and peripheral tissues. We present two siblings diagnosed with NF1 who presented at an early age with isolated menarche.

Case Presentation: Sibling 1 – A 7-year-old patient was referred with concerns regarding recurrent cyclical vaginal bleeding for 3 months. Bleeding was moderate and typically lasted 2-3 days. On examination the patient was prepubertal (P1, B1, A1) with no evidence of focal neurological deficit. Examination under anaesthetic of the genitalia identified no focal cause of the bleeding. The patient had been diagnosed with NF1 at 4 years of age based on family history, multiple café au lait spots and an MRI scan showing a $15 \times 11 \times 10$ mm optic glioma. She required no medications and

had mild learning difficulties. A gonadotropin releasing hormone (GnRH) test showed a prepubertal response (FSH peak 9.7 IU/L, LH peak 3.4 IU/L) and ultrasound of the pelvis revealed pre-pubertal uterine and ovarian appearances. The patient was managed conservatively and puberty was established at 12 years of age.

Sibling 2 – Five years later the 6-year-old sister of patient 1 presented with recurrent cyclical vaginal bleeding. On examination the patient was prepubertal. Further assessment under anaesthetic showed no focal cause of bleeding. The patient had been diagnosed with NF1 at 2 years of age based upon family history and cutaneous lesions. Serial cranial MRI scans were normal. Her GnRH test showed FSH dominant response (LH peak 3.5 IU/L, FSH peak 9.4 IU/L). Pelvic ultrasound showed ovarian volumes of 0.5ml and 0.7ml with a pre-pubertal uterus without an endometrial echo. The patient was managed conservatively and remains under active follow-up.

Conclusion: NF1 associated optic glioma has been previously associated with central precocious puberty. We describe two siblings with a clear history of premature isolated menarche but no evidence of central precocious puberty. Although the mechanism causing isolated menarche has not been established, this is an important association and adds to the understanding of phenotypes associated with NF1.

Case Report: A boy of 3,2 years- old -boy presented to our pediatric endocrinology unit for short stature. He was born at term after an uneventful pregnancy with 3,010 kg and 50 cm. His development was normal. He has familial Mediterranean fever. Parents are non-consanguineous and healthy. The mother's height is 156,3 cm and the father's height is 162 cm (target height -2.2SDS). At first examination his height was 86,4 cm (-2,8 DS), weight 11,05 kg and head circumference 46,8 cm (-3,4 DS). He had no dysmorphic features. The Tanner stage was A1P1G1 with 2 ml testes bilaterally. His growth chart showed a slow postnatal growth. Laboratory analysis showed a normal thyroid function (free T4 18,6 pmol/l), IGF1 was normal for age (67 ng/ml and 71 ng/ml), insulin tolerance test showed a good response for both growth hormone and cortisol (GH peak 7,44 ng/ml and cortisol peak 561 nmol/l). Microarray analysis showed a heterozygous deletion of 14q22.3 including the whole OTX2 gene. Both parents had normal microarray results. Cerebral MRI showed a malformation of the pituitary region, with an almost absent sella turcica, normal dimension of the anterior pituitary, with ectopic posterior pituitary gland, a very thin pituitary stalk and no optic nerve malformation. Ophthalmological examination showed no eye malformation or vision problem in our patient.

In conclusion we present on the case of a boy with heterozygous OTX2 deletion who harbors absent sella turcica, ectopic posterior pituitary but neither hormonal deficiencies nor eye malformation.

P2-237

Heterozygous OTX2 deletion in a boy with normal eye development and normal pituitary function

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Introduction: *Orthodenticle homeobox 2* (OTX2) is a transcription factor that plays a critical role in brain and eye development. Heterozygous deleterious mutations in this gene lead to eye malformation such as anophthalmia, microphthalmia, coloboma or optic nerve hypoplasia, normal or hypoplastic pituitary gland and normal or ectopic posterior pituitary gland with isolated growth hormone deficiency or combined pituitary hormone deficiency. There is no genotype – phenotype correlation. Patients with heterozygous OTX2 deletion without eye or pituitary development anomaly have never been reported.

We report on a 3,2 years old boy with a de novo heterozygous deletion of OTX2 without hormonal deficiency or eye malformation.

P2-238

Risk Factors for Hypogonadism in Patients with β-Thalassemia Major: A Cross-sectional study

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Objective: To investigate the prevalence of hypogonadism in patients with β-Thalassemia Major (β-TM) and explore the risk factors.

Method: 42 β-TM patients (≥ 10 years old) were investigated by questionnaire, physical examination and laboratory examination to evaluate their stages of puberty development and sex hormone level. And then, effects of age, the beginning age of chelation, iron overload, genotype and other factors on pubertal development in β-TM patients were analyzed.

Result: Hypogonadism was one of the most common endocrine complications in β-TM patients and the incidence rate was 57.14%, and there was no difference between male and female. Age, the beginning age of chelation, serum ferritin, hepatic T2*, cardiac T2*, genotype, liver function, vitamin D level and diabetes mellitus were important factors influencing puberty development of β-TM patients. The multivariate logistic regression analysis showed that cardiac T2* and age were independent risk factors for hypogonadism in β-TM patients.

Conclusion: Hypogonadotropic hypogonadism is the most common endocrinopathy in β-TM patients. Although it is rarely life threatening, it can severely impair the quality of life. Iron overload is a significant risk factor. Hence, proper and effective iron chelation therapy is essential.

P2-239**Radiation therapy for children with medulloblastoma: Growth and thyroid sequelae**

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Background: Medulloblastoma is the most common malignant pediatric brain tumor. Although survival has improved with oncological therapy, late effects such as endocrine consequences are common, especially growth failure and thyroid dysfunction.

Methods: Children diagnosed with medulloblastoma in a pediatric hospital between 2004 and 2014 were studied and followed until 2019. Statistical analysis was performed to estimate the effect of radiotherapy (RT) on growth and thyroid disorders.

Results: Fifty-six patients (39 boys, 17 girls) were reviewed. The mean age at diagnosis was 5.2 years (IQR:3.0-8.1). Forty-three were assessed by pediatric endocrinologists for 3.5 years (IQR:0.6-7.3), of which 14 are still being followed in our department.

Forty-five patients received RT and endocrine alterations were significantly more frequent afterwards ($p=0.03$), especially for growth hormone (GH) and thyroid function disorders ($p<0.05$). The mean dose to the posterior fossa was 54.3 Gy (IQR:54-60) and to the crani spinal region 30.9 Gy (IQR: 23.4-36). Median age at the time of radiotherapy was 5.8 years (IQR:4.2-9.1).

GH deficiency was the most common sequelae (21 patients) after a mean of 3.8 years of RT (IQR:3.0-5.8), followed by hypothyroidism (14=primary, 5=secondary) after 3.0 years of age (IQR:1.5-5.1). Patients who received RT and developed hypothyroidism also presented ultrasound alterations: 48% with reduced size of thyroid and 31% with altered echogenicity. There was a strong association between radiotherapy and hypothyroidism, $p=0.01$.

Only 12 patients received GH treatment (12/21). The mean GH peak after clonidine and insulin tolerance test was 2.5 µg/L (IQR:0.7-3.5) and 1.2 µg/L (IQR:0.5-3.5), respectively. GH therapy was stopped after a mean of 3.2 years (IQR:2.0-5.0) of finalizing oncological therapy and at 12.1 years of age (IQR:9.1-12.6); only 45.5% were prepubertal. Growth velocity before GH replacement was -3.7 SDS (IQR:-4.4,-1.8) and after one year of treatment +1.0 SDS (IQR:-0.3,+2.3). Mean time of treatment was 2.4 years (IQR:1.0-4.5). Six achieved final height -2.2 SDS (IQR:-3.3,-1.6); -2.0 SDS (IQR:-2.7,-0.8) corrected for their target height.

Conclusions: Radiotherapy is significantly linked to hormonal deficiencies. Long-term follow up is essential especially in the first years after radiotherapy.

1. Hypothyroidism is correlated to radiotherapy and the volume of the gland is reduced in almost half of these patients.

2. Not only radiotherapy may have a role in incomplete catch-up growth, but also other oncological therapies.

P2-240**Bone age determination in girls with early puberty and limitations of adult height prediction: Can automated evaluation (BoneXpert™) be a solution?**

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Introduction: One of the factors affecting the treatment decision in early puberty is bone age (BA) evaluation and adult height prediction (AHP), accordingly. These calculations have certain limitations. In this study, we aimed to compare the AHP results calculated by Bayley-Pinneau (BP) and Roche-Wainer-Thissen(RWT) methods based on BA evaluation by using Greulich-Pyle(GP) atlas and BoneXpert™ software.

Methods: A total of 77 girls (6.1-10.8 years of age) who presented with early puberty suspicion between June 2016 and November 2018, were included in the study. At the time of presentation, BA was determined by a pediatric endocrinologist by using GP bone age atlas (Standard BA). The same X-rays were also analyzed by BoneXpert software program and bone age was determined by GP (BXpertBA-GP) and TW (BXpertBA-TW) methods. Adult height prediction was calculated by using a national online program named ÇEDD-ÇÖZÜM. Three BA evaluations and two AHP methods (BP and RWT) were used to calculate predicted adult heights (PAH) of participants, thereby 6 different predictions were made (PAH₁: BP method with standardBA-GP, PAH₂: RWT method with standardBA-GP, PAH₃: BP method with BXpertBA-GP, PAH₄: RWT method with BA-GP, PAH₅: BP method with BXpertBA-TW, PAH₆: RWT method with BXpertBA-TW)

Results: The mean age of the participants was 8.7 years, while the mean standard BA was 9.98 years, the mean BXpertBA-GP was 9.87 and the mean BXpertBA-TW was 9.51 years. There was no significant difference between the mean standard BA and BXpert BA-GP. However, BXpert BA-TW was significantly lower than the other two BAs ($p <0.001$). The mean actual height of the participants was 136 cm while median height SDS was 1.01. The mean PAH₁ was similar to PAH₃(161.3 vs 162.2 cm), however PAH₁ was significantly lower than PAH₂ (162.6 cm), PAH₄(162.5 cm), PAH₅(164.3 cm), PAH₆(163.5 cm) ($p<0.008$). The mean PAH₁ was significantly lower than mean mid-parental height of the participants 161.3 vs 163.3 cm, $p<0.007$.

Conclusions: The PAH which was calculated by the most commonly used BP method based on Standard BA-GP is the lowest, however it is impossible to determine which method is most accurate until the participants achieve their final heights. We think that, it would be more reasonable to take a range rather than only one result for PAH into consideration before making a decision on treatment.

P2-241

Effect of gonadotropin-releasing hormone agonist treatment on final adult height in boys with idiopathic central precocious puberty

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Purpose: Central precocious puberty (CPP) is less common in boys than girls; very little data is reported on long-term effects of gonadotropin-releasing hormone analog (GnRHa) treatment in boys with CPP. The aim of the study was to evaluate the impact of treatment with GnRHa on adult height (AH) and body mass index (BMI) in boys with idiopathic CPP.

Subjects and Methods: In 18 boys with confirmed diagnosis of idiopathic CPP, auxological [height, height standard deviation score (HT-SDS), bone age (BA), HT prediction] and endocrinological parameters were obtained at baseline, at 6 months and at 1 year after GnRHa treatment, and at the time of reaching the final adult height in boys with CPP.

Results: The duration of GnRHa treatment in boys with idiopathic CPP was 23.6 ± 9.1 months. AH, reached after GnRHa treatment was 171.7 ± 4.8 cm, it was similar to the pretreatment predicted AH (PAHav) for average tables of Bayley and Pinneau (BP). Also it was similar to the target height (TH, 171.0 ± 4.0 cm). The pretreatment PAH for accelerated tables of BP (179.6 ± 6.2 cm) was overestimated than AH ($P < 0.001$). Hormone levels reduced during treatment, increased to normal after GnRHa treatment. BMI-SDS for chronological age was decreased during and after GnRHa treatment. Regression analysis between AH and several parameters showed a positive correlation with TH, and PAHav, PAH, HT, and HTSDS at diagnosis, 6 months and 1 year after treatment. In multiple regression analysis of the variables that affect the AH, PAHav at 6months after GnRHa treatment had positive correlation with AH ($P < 0.001$).

Conclusion: The present data indicate that GnRHa treatment can improve final adult height into the range of target height without significant adverse effects in boys with CPP.

P2-242

Evaluation of the alpha2-adrenergic receptors stimulation effect on prolactin secretion, based on the result of the test with clonidine used in the diagnosis of children with short stature

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Introduction: Prolactin (Prl) - secreting cells and growth hormone (GH) - secreting cells are derived from the common somatotrophinotropic cells. Prl secretion depends primarily on the inhibitory effects of dopamine and the stimulatory effects of TRH and estrogens. The effects of other factors, especially the stimulation of the adrenergic system, are not well recognized. It is known that presynaptic stimulation of the alpha2-adrenergic receptor results in suppression of noradrenaline secretion. It is presumed that at the same time, the secretion of Prl is inhibited, but this has not been fully explained. On the other hand, stimulation of the alpha2-receptor is widely used in the diagnosis of growth hormone deficiency (GHD) in children. Clonidine is the most commonly used factor. Clonidine, by stimulation of the presynaptic alpha2-adrenergic receptor, in addition to inhibiting the release of noradrenaline, simultaneously stimulates the secretion of somatotropin (GHRH) from the hypothalamus, which in turn stimulates the synthesis of GH.

The aim of the study was to evaluate the effect of stimulating alpha2-adrenergic receptors after clonidine administration on Prl secretion, as well as to assess the differences in response to the abovementioned stimulation in groups of children with normal and decreased GH secretion (ISS and GHD groups).

Material and Methods: The serum concentrations of Prl and GH at individual time points during the 2-h stimulation test for GH secretion after oral clonidine administration at a dose of 0.15 mg/m^2 were assessed. The test was carried out for diagnostic purposes in 49 children (mean age \pm SD: 9.55 ± 3.48 yrs) with short stature (height <-2.0 SD). In 29 children ISS and in 20 - GHD were diagnosed.

Results: In both GHD and ISS children, there was no significant reduction in Prl secretion after clonidine administration at any of the time points. Prl concentration decreased insignificantly at 30 minute after clonidine administration and then remained at the same level at subsequent time points.

In both groups of children, no differences were found in the mean concentration of Prl at individual time points. There was no correlation between the concentration of Prl and GH during the test in GHD group, however, there was a significant positive correlation between the concentrations of both hormones at the 90th minute of the test in children with ISS.

Conclusions: Short-term adrenergic stimulation of alpha2-receptors (after oral clonidine administration) does not appear to affect Prl secretion in children with short stature in both the ISS and GHD groups.

P2-243**A case of severe recurrent hypoglycemia after traumatic brain injury**

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A 14-year-old male had a severe traumatic brain injury (TBI) after a motorcycle accident 11 months ago. He underwent craniotomy and was admitted in ICU. Two months later, he was diagnosed as refractory epilepsy. Three episodes of seizure were related to low blood sugar (blood sugar 10-20 mg/dL). He had inadequate intake due to fatigue and loss of appetite. Liquidized food via the enteral feeding route every 4 hours was used to prevent hypoglycemia. Levetiracetam (Keppra) 250 mg twice a day was used to treat seizures. However, epilepsy was not controlled by medication. He was referred to a Pediatric Neurologist. MRI of the brain demonstrated gliotic and encephalomalacia changed at anterior left frontal lobe and left temporal lobe. Severe atrophic changed of the pituitary gland, without mass lesion. (Figure1) Electroencephalography revealed focal epileptic disorder arising from the left frontopolar area. Laboratory showed FT4 0.29 ng/dL, FT3 1.89 pg/mL, and TSH level of 3.80 mIU/L. These were consistent with central hypothyroidism.

At our hospital, the patient was being bedridden. His weight was 39.5 kg, his height was 156.8 cm. The laboratory test revealed panhypopituitarism; central hypothyroidism, GHD, central adrenal insufficiency, hypogonadotropic hypogonadism. (Table1). He had no symptom of central DI.

Prednisone and thyroxine were started. The anti-epileptic drug was continued. Later, he had a normal appetite and his weight increased 5 kilograms in a month. He had no episode of hypoglycemia and seizure.

Discussion: Signs and symptoms associated with hypopituitarism often mimic the sequelae of TBI. Therefore, hypopituitarism is likely to be underdiagnosed.

In our case, we considered recurrent severe hypoglycemia as the result of central adrenal insufficiency and GHD which are in counter-regulation mechanisms of hypoglycemia. Moreover, central adrenal insufficiency and central hypothyroidism caused the consequences of appetite and body weight.

Conclusion: We reported the case of panhypopituitarism following the severe TBI with an unusual presentation as hypoglycemia. In the case of severe TBI, the hormonal testing should be conducted, and then routine hormonal screening tests should be evaluated.

	Results	Reference range	Units
TSH	2.49	0.20 to 4.00	mIU/L
FT3	1.47	1.60 to 4.00	pg/mL
FT4	0.18	0.8 to 2.3	ng/dL
GH	<0.05	0-1	ng/mL
IGF1	26.8	187-510	ng/mL
ACTH	13.0	0-46	pg/mL
Cortisol	<1	ug%	
FSH	0.2	1-8.4	IU/L
LH	<0.10	1-10.5	IU/L
Testosterone	<0.087	5.9-24.7	nmol/L
Na	135	135-145	mmol/L

Sex Differentiation, Gonads and Gynaecology or Sex Endocrinology

P2-244**The Evolving Role of Whole Exome Sequencing in the Diagnosis of Disorders of Sex Development (DSD)**

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Background: Disorders of sex development (DSD) are classified as a congenital discrepancy between external genitalia, and gonadal and chromosomal sex. Despite extensive laboratory and imaging investigations, the etiology of DSD is unknown in more than 50% of patients. We aimed to evaluate the etiology of DSD using whole exome sequencing (WES) technique.

Methods: Eleven patients with DSD (ten with 46,XY and one with 46,XX genotype) who underwent comprehensive laboratory investigations, including candidate gene approach sequencing, were enrolled. WES was performed for the probands and their parents.

Results: In 5 of the 11 patients, a pathogenic mutation was identified that explained the phenotype. In an 11-y-old 46, XX-DSD girl, a missense mutation in cytochrome P450 oxidoreductase (*POR*) was identified. In the other four 46, XY.

Patients: a 2-y-old infant with severely delayed psychomotor development had a previously reported *de-novo* heterozygous missense mutation in chromodomain-helicase-DNA-binding protein 7 (*CHD7*); an 8-y-old boy, previously reared as a girl, had a novel

homozygous missense mutation in *HSD17B3*; a 13-y-old boy had a novel *de-novo* splice mutation in *WT1*, and an 11-y-old boy had a novel *de-novo* mutation in bone morphogenetic protein 4 (*BMP4*). Identification of the etiologies of DSD in these patients enabled us to provide accurate genetic consultations for the families and appropriate therapy for the patients. In 4 patients, no potentially pathogenic variants were found in genes known to cause DSD and in 2 patients, variants of unknown significance were identified.

Conclusions: WES played a crucial role in the diagnosis of DSD; still, in 50% of the cases, no obvious etiology was found. Using WES is cost-effective, make extensive endocrine testing unnecessary and assist parents and physicians in making early and appropriate decisions regarding gender assignment.

P2-245

Etiological structure disorders of sex development 46, XY by one center

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Objective: To study structure disorders of sex development (DSD) 46,XY by one center.

Subjects and Methods: It was included 60 patients with diagnosis DSD 46,XY at birth to 18 years. For all patients was conducted structural evaluation of the external (by External Masculinization Score, EMS, 0-12) and internal genitalia (by pelvic ultrasound, n=60, laparoscopy, n=20), hormonal research (testosterone, dihydrotestosterone, androstendione, anti-Mullerian hormone, AMH, inhibin B, follicle-stimulating hormone, luteinising hormone) in mini-puberty (n=28), neutral period (n=21) and puberty (n=11), molecular genetic studies Ion Torrent custom Ampliseq_DSD (n=37) and gene such us AR (n=14), SF1 (n=2), SRY (n=3), CYP21 (n=2), WT1 (n=2), histology of gonads removed (n=23 by 15 patients).

Gonadal Dysgenesis Criteria: derivats Mullerian duct, AMH < 55 ng/ml in mini-puberty and AMH < 85 ng/ml in neutral period [Edelsztein N.Y et al].

Results: A definitive diagnosis was received in 56% (33/60) of children with 46,XY DSD: disorders of gonadal (testicular) development - 37% (22/60), disorders in androgen synthesis or action - 15% (9/60), persistent Mullerian duct syndrome - 2% (1/60) with homozygous mutation AMH, Smith-Lemli-Opiz syndrome - 2% (1/60) with heterozygous mutation DCHR7.

Disorders of gonadal development include complete gonadal dysgenesis in 13% (3/22) cases (pathological mutation WT1, n=1; SRY, n=2), in 82% (18/22) of cases – partial gonadal dysgenesis (pathological mutations SF1, n=2 u SRY, n=1; mutations in the genes SF1, n=1, ESR2, n=2, LHCGR1, n=1 pathological significance of today is not known), in 5% (2/22) – ovotesticular DSD (mutation ZFPM2, n=1 with pathological significance of today is not known).

Disorders in androgen synthesis or action presented by total (44%, 4/9) and partial (56%, 5/9) androgen insensitivity syndrome in 100% patients with pathological mutations gene AR.

While y 44% (27/60) of patients didn't have verified variant of nosological pathology (mutation in genes LHX1, n=1, HSD17B3, n=1, AR, n=1, ZFPM2, FOXF2, n=1 with pathological significance of today is not known).

Conclusion: Completed complex survey including molecular genetic analysis allowed to verify nosological variant of DSD 46,XY only in 56% (33/60) of patients.

Rating of nosological variants of DSD 46,XY by frequency: partial gonadal dysgenesis (67%, 22/33), androgen insensitivity syndrome (27%, 9/33), total gonadal dysgenesis (10%, 3/33), persistent Mullerian duct syndrome (3%, 1/33), ovotesticular (3%, 1/33), Smith-Lemli-Opiz syndrome (3%, 1/33). Mutations in genes involved in gonadal development detected in 28% (17/60) patients, dominant mutations by frequency – AR (53%), SRY (17%), SF1 (12%), WT1 (6%), AMH (6%), DCHR7 (6%).

P2-246

Comparison of growth status, level of blood glucose and lipid metabolism in SGA and AGA girls with central precocious puberty

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Background: Several studies have shown that born small for gestational age (SGA) children have earlier precocious puberty, progress faster, and are less likely to gain target height in adults than children born appropriate for gestational age (AGA). Moreover, SGA children are more prone to metabolic disorders - obesity, diabetes and cardiovascular disease.

Objective: To compare the physical development status, serum lipid levels, fasting blood glucose, fasting insulin levels and HOME-IR in SGA and AGA groups with central precocious puberty (CPP).

Methods: A retrospective analysis of 322 girls with CPP was divided into AGA group (304 cases) and SGA group (18 cases) according to gestational age and birth weight. The chronological age, bone age and Tanner stage were matched in the two groups. Physical index such as height, weight and BMI, as well as blood lipid levels, fasting blood glucose, insulin levels and HOME-IR were compared between the two groups.

Results: Height, weight, and BMI in the SGA group (129.44 ± 8.06 cm, 25.83 ± 4.16 kg, and 15.40 ± 2.08 kg/m²) were significantly lower than those in the AGA group (135.00 ± 7.63 cm, 31.50 ± 6.31 kg, and 17.16 ± 2.31 kg/m²), and the differences were statistically significant ($P<0.05$). The fasting blood glucose, insulin levels and HOME-IR in the SGA group were lower than those in the AGA group (4.66 ± 0.52 mmol/L vs. 4.73 ± 0.44 mmol/L, 5.65 ± 3.68 mIU/L vs. 6.81 ± 3.56 mIU/L, 1.20 ± 0.85 vs. 1.44 ± 0.78 , respectively), but the difference was not statistically significant ($P>0.05$). The triglyceride level in the SGA group was higher than that in the AGA group. The levels of total cholesterol, HDL and LDL in SGA group were

lower than those in AGA group. There was no significant difference in triglyceride and HDL between the two groups ($P>0.05$). The difference between cholesterol and LDL was statistically significant ($P<0.05$). However, the blood lipids and blood glucose in both groups were within the normal range.

Conclusion: The chronological age and bone age of precocious puberty in SGA and AGA were similar, however, the height, weight and BMI of the SGA group were significantly lower than those of the AGA group. Therefore, children in SGA with CPP have a higher risk of short stature in adulthood. In this study, blood glucose and lipid metabolism were normal in the two groups, but it is necessary to regularly follow-up and assess growth and metabolic markers in SGA children.

P2-247

Does the anogenital distance predict outcome of Hypospadias repair?

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Purpose: The anogenital distance (AGD) is androgen action dependent. It is sexually dimorphic and seems to be shorter in androgen-action related diseases like hypospadias. In this study we sought to determine whether the AGD is predictive for surgical outcome in hypospadias repair.

Material and Methods: Patients were collected prospectively. AGD was measured in OR prior to surgery by 2 surgeons (blinded, each 3 times). Outcome parameters were defined as: 1.) complications (fistula, breakdown, glans dehiscence, redo surgery) and 2.) need for staged repair. There were 208 prepubertal boys: 119 controls 2.38yrs (0.02-10.2) and 89 hypospadias (55 distal hypospadias 2.74yrs (0.07-9.67) and 34 proximal hypospadias 2.45yrs (0.58-9.76). Mean follow-up was 1.1yrs.

Results: There was no difference in AGD in controls and mild hypospadias. Severe hypospadias had a significantly shorter AGD ($p=0.003$). AGD was significantly shorter in patients undergoing staged repair (37mm vs. 26mm, $p=0.001$). AGD was significantly shorter in patients who developed postoperative complications (38mm vs. 29mm, $p=0.04$).

Conclusions: Shorter AGD predicts higher complication rate and the need for more extensive surgery. Hypothetically, a short AGD resembles impaired intra uterine androgen action (low androgens, androgen receptor problems, counteracting endocrine disruptors, and unknown genetic androgen interaction). These fetal androgen deficiencies may be reflected in hypospadias minor tissue quality resulting in delayed wound healing, inflammation and a higher complication rate or more difficult surgery resulting in staged repair.

P2-248

GnRH Analogues Use In Post-Pubertal Adolescents With Gender Dysphoria Causes A Reduction In Bone Density Values

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Objectives: Gender Dysphoria (GD) occurs when a person's gender identity differs from their biological sex. Medical interventions may be considered at puberty. This involves the use of a GnRH analogue (GnRHa) for at least one year prior to considering cross sex hormones from 16 years of age. We assessed the bone density and body composition changes after the use of GnRHa in individuals with GD.

Methods: All individuals have standardised assessments including pubertal stage, bone & hormone profile, body composition and bone density at baseline and at annual intervals. Pubertal suppression was with intramuscular administration of GnRHa. Bone density was expressed as BMD g/cm² and values at the lumbar spine (L2-L4), total body (TBBMD) and total body less head (TBLH) were recorded. To correct for bone size, a Bone Mineral Apparent Density (BMAD) g/cm³ was calculated. All adolescents with a diagnosis of GD in Tanner stage 4 or 5 were included.

Results: Seventy seven post-pubertal adolescents, had GnRHa for a mean age of 1.2 years. 41 were assigned female at birth (AFAB) and 36 assigned male at birth (AMAB). There was a significant reduction in lumbar spine BMAD; AFAB -0.10 SDS to -0.74 SDS ($p<0.05$); AMAB -0.67 SDS to -1.35 SDS ($p<0.05$). There was also a significant reduction in TBBMD in AMAB (-0.02 SDS to -0.72 SDS) & TBLH (-0.35 to -0.57 SDS), whereas AFAB had a downward trend for TBBMD and TBLH, but this was not significant. The BMI SDS increased slightly by 0.1 SDS ($p=0.19$) and this was associated with an increase in fat mass of 5.1% in the whole group and decrease in muscle mass by 4.8% ($p<0.05$). AMAB had an increase in fat mass by 8.1% and 7.8% reduction in lean mass, whereas AFAB had an increase in fat mass by 2.4% and decrease in lean mass by 2.1%.

Conclusions: This is the largest report of bone density changes in adolescents with GD treated with GnRHa in a homogenous population. It demonstrates a reduction in bone density (spine and total body) in post-pubertal adolescents treated with GnRHa. After one year treatment, there is an increase in fat mass, reduction in lean mass and reduction in lumbar spine and total body bone density values. The clinical significance of these short term changes remains to be determined and whether these can be reversed by the initiation of cross sex hormones.

P2-249

11-oxygenated androgens may be related to the virilization of female external genitalia due to the maternal androgen-producing adrenal tumor

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Background: Fetal-derived androgen excess, such as 21-hydroxylase deficiency (21-OHD), is a major cause of 46,XX disorders of sex development (DSD), but there are rarely due to maternal androgen excess such as that caused by adrenal tumors or luteoma. Recently, in addition to the classical androgen synthesis pathway, the alternative androgen synthesis by backdoor pathway and 11-oxygenated steroids has been reported for virilization of female patients with 21-OHD. We have reported 46,XX DSD due to maternal androgen-producing adrenal tumors with mild masculinization signs in the *Journal of the Japan Pediatric Society*. The purpose of this study was to examine the relationship between maternal androgen levels and fetal external genitalia in our patients.

Patients and Methods: The female patient was diagnosed as 46,XX DSD with degree of virilization with Prader grade 3-4. Her mother was 30 years old and had noticed hirsutism before and during pregnancy, without other masculinization signs. She developed gestational diabetes mellitus and pregnancy-associated hypertension and gave birth via emergency cesarean section at 30 weeks of gestation. She was diagnosed with an androgen-producing adrenal tumor and Cushing syndrome at 8 months after delivery because of the virilization of her female infant's external genitalia and continuing her hirsutism. The tumor was removed by laparoscopic surgery, and the histology indicated an adrenal adenoma. With the use of gas chromatography/mass spectrometry (GC/MS), urinary steroid profiles were measured in maternal urine before tumor resection.

Results: Maternal serum DHEA-S, androstenedione and testosterone levels were only slightly high at 571 µ/dL, 2.26 ng/mL, and 81 ng/dL, respectively. Analysis of urinary steroid profiles revealed high DHEA metabolite values, and 11-OH androstenedione metabolite levels, which were 4 times higher than the upper limit, and androstenedione metabolite levels which were remained at 1.5 times higher than the upper limit.

Discussion & Conclusion: Maternal serum androstenedione and testosterone levels could not explain the severe virilization of the female infant's genitalia. According to the results of maternal urinary steroid profiles, virilization of the external genitalia may be caused by the alternative pathway via 11-oxygenated steroids. Although we were unable to measure maternal serum

11-oxygenated steroids, 11-oxygenated androgens may be related to the virilization of female external genitalia due to the maternal androgen-producing adrenal tumor.

P2-250

High prevalence GnRH receptor mutations in Russian patients with idiopathic hypogonadotropic hypogonadism

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Background: GNRHR gene mutations are responsible for development to normosmic idiopathic hypogonadotropic hypogonadism (iHH) and known to be the most frequent cause of this condition. Nevertheless, the reported frequency of GNRHR mutations in iHH patients estimated to be as low as 3-6%.

Objective: To evaluate the frequency of GNRHR gene defects in a heterogeneous group of Russian patients with iHH and described the phenotype of patients with identified defects.

Methods: 144 patients with iHH (119 boys, 25 girls) were included in the study, 51 of them had olfactory impairment. 'Hypogonadotropic hypogonadism panel' genes were sequenced using a custom Ion Ampliseq gene panel and PGM semiconductor sequencer (Ion Torrent). The panel included genes: CHD7, DNMT3L, DUSP6, FGF17, FGF8, FGFR1, FLRT3, GNRH1, GNRHR, HS6ST1, IL17RD, INSL3, KAL1, KISS1, KISS1R, LHB, NELF, POLR3B, PROKR2, RBM28, SEMA3A, SPRY4, TACR3, WDR11, GREAT, TAC3, KAL4, NR0B1, POLR3A, MKRN3. Interpretation of the sequencing results and assessment of the pathogenicity of sequence variants were performed according to the ACMG guidelines (2015).

Results: 4 sequence variants in GNRHR were detected in 15 patients (11%), 4 girls and 11 boys. The most frequent mutations in our group were p.R139H (n=13), p.M1T (n=6) and p.R262Q (n=3). Mutations in GNRHR were detected as part of digenic defects in 2 cases: with a hemizygous mutation p.E156Gfs5X in KAL1; with heterozygous mutation p.V248M in FGFR1.

One patient was hyposmic with a digenic defect in GNRHR and KAL1.

Conclusions: A high percent (10%) iHH due to mutations in GNRHR gene was detected in the heterogeneous group of patients (normosmic iHH and KS). 13 cases of hypogonadism were completely explained by the identified changes in GnRH receptor gene. In a patient with the digenic defect in GNRHR and KAL1 genes, hypogonadism can be due to changes in each of these genes. The defects in GNRHR and FGFR1 genes probably potentiate each other

3 β -HSD2 deficiency due to compound heterozygosity of a missense mutation (p.Thr259Met) and a frameshift deletion (p.Lys273ArgFs*7) in an under-virilized infant male with salt wasting

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Objectives: To describe clinical, hormonal and genetic findings of an under-virilized infant male, 13 month old, of afghani origin, presented at the emergency department with salt-wasting adrenal crisis.

Case Report: The patient, a 13 month old male infant, presented at the emergency department with complaints of vomiting and fever. Physical examination was significant for severe dehydration along with perineal hypospadias, bifid scrotum, penile chordee and undescended left testicle. From history he was under cortisone treatment that was discontinued 15 days prior to referral to our hospital. Laboratory evaluation revealed hyponatremia, Na: 130 mEq/L (135-145 mEq/L) with concurrent hyperkalemia, K: 5.5 mEq/L (3.5-4.5 mEq/L). He was admitted to the pediatric care unit and started on hydrocortisone, fludrocortisone, and sodium chloride supplementation. Steroid hormone testing obtained before treatment revealed a complex pattern suggestive of congenital adrenal hyperplasia (CAH) due to 3 β -HSD deficiency. Hormonal determinations revealed the following abnormal values: DHEA-S: 13.35 (<0.600) μ gr/ml, 17-OH-Progesterone: 35.07 (0.200-0.800)ng/ml, Testosterone: 0.946 (<0.025)ngr/ml, Cortisol: 1.15 (6.2-23.00) μ gr/dl. Chromosomal karyotype was 46,XY. Scrotal ultrasound revealed the right testicle in the scrotal area (1.82x1.34x0.92) cm (Vol: 1.12cm³) and the left testicle in the upper inguinal area (1.38x0.89x0.93) cm (Vol: 0.58 cm³), both harboring microcalcifications. Molecular analysis performed by next generation sequencing revealed a missense mutation : c.776C>T, p.Thr259Met, transmitted by the mother and a frameshift deletion: c.818-819delAA, p.Lys273ArgFs*7 transmitted by the father. Both mutations are described as pathogenic. The patient recovered from his acute illness, was discharged home on steroids. In the near future he will have urologic surgery to correct his urogenital anomalies.

Conclusions: Deficiency of 3-beta hydroxysteroid dehydrogenase type II (3 β -HSD2) is a rare autosomal recessive form of congenital adrenal hyperplasia (CAH). More than 40 mutations have been found in the HSD3B2 gene causing 3 β HSD2D. To the best of our knowledge, our patient is the first under-virilized male with severe salt wasting presenting compound heterozygosity of missense c.776C>T, p.Thr259Met and frameshift deletion: c.818-819delAA, p.Lys273ArgFs*7.

Clinical evaluation of newly developed scoring system for DSD (DSD-SS): Association of DSD-SS with assigned gender in 45,X/46,XY mosaicism

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Background: We have proposed a simple and comprehensive scoring system to evaluate clinical features of differences/disorders of sexual development (DSD); however, its clinical evaluation has not been performed.

Aim: To evaluate the association between this newly proposed DSD scoring system (DSD-SS) and assigned gender in patients with 45,X/46,XY mosaicism.

Methods: DSD-SS involves evaluation of the external and internal genitalia, and gonads consisting of a) growth and b) fusion of scrotum/labia majora, c) glans penis development, d) urethral orifice position, e) presence or absence of the urogenital sinus, f) presence or absence of the uterus, and g) gonadal position (scrotal, inguinal, or abdominal). Each component has two to four ranks (for a score from 0 to 6). The sum of each score was calculated with complete male phenotype being attaining the score of 42. To determine the association of DSD-SS and assigned gender, we retrospectively evaluated 46 subjects with 45,X/46,XY mosaicism through their medical records. The scoring of external genitalia was based on direct evaluation of photographs. This study is approved by institutional ethical committees.

Results: Twenty-one subjects were male-assigned (M) and 25 were female-assigned (F), the latter of which included 12 subjects with Turner syndrome (TS). Subjects with TS were excluded from the subsequent analysis because they showed complete female external genitalia, the presence of uterus, and intra-abdominal gonads (score 0). The average score in M (N=21) was 25 and this was significantly higher than that of F (N=13)(score 10). Ninety-five percent of M scored equal to or above 19, whereas the score of 91% of F was lower than 19. The score of each component of external genitalia showed significant overlaps between M and F; however, total score of external genitalia showed minimal overlaps, suggesting the comprehensiveness of DSD-SS. All the F possessed uterus, indicating that the presence of uterus is an important factor for female assignment. Half of M showed the presence of uterus, but the total score of external genitalia in M was higher compared to F irrespective of the presence of uterus. The score of gonadal position showed significant overlaps between M and F.

Conclusion: The newly developed DSD-SS is useful in comprehensively evaluating the clinical features and DSD-SS based scoring well corresponded to the assigned gender in 45,X/46,XY mosaicism.

This is a side-by-side submission with the presentation by Nagamatsu et al. (submission No: 526)

P2-253**Complexities of diagnosis in 17-beta-hydroxysteroid dehydrogenase deficiency and implementation of next generation sequencing in guiding management decisions – Case series of six patients**

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17-beta-hydroxysteroid dehydrogenase (17-beta-HSD3) deficiency is an autosomal recessive 46XY disorder of sex development (DSD), which results in impaired gonadal androstenedione conversion to testosterone. The phenotype ranges from female to ambiguous genitalia, with wolffian-duct structures and testes. HCG stimulation tests assess testosterone biosynthesis, though biochemical results in confirmed 17-beta-HSD3 deficiency may overlap with gonadal dysgenesis making diagnosis challenging. Therefore, additional molecular genetic diagnostics will help guide surgery and sex of rearing discussions.

We report six 46XY DSD patients with confirmed 17-beta-HSD3 deficiency. Four patients were diagnosed <12months of age: one identified antenatally due to discordant karyotype and ultrasoundography, two identified at delivery due to ambiguous genitalia, and one identified aged three months during elective herniotomy. The two adolescent patients presented with progressive virilisation, causing significant emotional distress, and primary amenorrhoea.

Of the four patients identified <12months, baseline immunoassay testosterone ranged between 1.1-12nmol/L. Three demonstrated low T:A ratio after HCG stimulation: (0.11, 0.7 and 0.84 respectively). Case 6's T:A ratio of >0.8 is discordant with literature stating that HCG-stimulated ratio <0.8 is consistent with 17-beta-HSD3 deficiency.

The time taken between initial identification of DSD and molecular genetic diagnosis ranged between 6weeks – 22months. Significantly longer times were experienced by patients presenting prior to 2014, when the 32 gene next generation sequencing (NGS) panel for DSD became available. Patients presenting during 2016-18 had a 4-5 month interval between presentation and molecular genetic diagnostic confirmation. The most recent cases in 2019 had the diagnosis confirmed within 9 weeks of presentation.

Decisions around sex of rearing in the infants and surgery (including gonadectomy) involved multidisciplinary team discussions. In two, parents elected to undergo bilateral gonadectomy. Unilateral gonadectomy was performed on case 2 during a herniotomy procedure when gonadal vessels and vas were inadvertently

divided, the gonad removed and sent for histopathology. The two adolescent patients elected to defer gonadectomy and were initially treated with combined GnRH analogue and oestrogen. One subsequently underwent gonadectomy three years later. All 6 patients have been raised female, and neither of the two adolescent cases have voiced gender dysphoria/disturbance concerns.

We highlight the difficulty interpreting both baseline and HCG stimulated plasma hormone levels, and how molecular genetic diagnosis through NGS is becoming integral to providing timely diagnostic information to patients and their families. Complex decisions regarding sex of rearing, gonadectomy and consideration for genital corrective surgery are best managed by an expert multidisciplinary team.

P2-254**Paediatric Health Assistance to Transsexual Minor in the Multidisciplinary Care Unit of the Basque Country (Spain)**

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In 2009, the National Health Service of the Basque Country created a Gender Identity Reference Unit (GIU-BC) to cover the health needs of the transsexual population with a multidisciplinary assessment: Psychiatry, psychology, endocrinology, plastic and reconstructive surgery. Pediatric endocrinologists and pediatric psychiatry were included in 2013.

Aim: To know the activity of Pediatric Endocrinology in the GIU-BC since 2013.

Patients and Methods: A retrospective/descriptive study was conducted to evaluate the endocrinological assistance offered to young patients with gender dysphoria/transsexuality in the GIU-BC. Epidemiological and clinical variables were studied. The GIU-BC follows the health care approach recommended by the Endocrine Society 2017⁽¹⁾ and the Working Group of the Basque Government 2016⁽²⁾. Transgender adolescents were treated with pubertal suppression (using gonadotropin-releasing hormone analogues) in stage 2 of Tanner, if possible, followed by the use of cross-sex hormones (estrogen or testosterone) at the age of 14-16 years. Monthly meetings scheduled to discuss the suitability of the physical and emotional situation of each patient before starting hormonal therapies.

Results: 60 children and adolescents with gender dysphoria or transsexuality were evaluated (55% assigned female sex) with an average age of 11.3±3 years (range 4-15). Pubertal development: 35% prepubertal, 18% Tanner II-III and 47% Tanner IV-V. The number of patients/year over time was: period 2013-2016: 10//

2017: 13// 2018: 37. The 77.3% of the children/adolescents made the social transition before attending the GIU. 6.7% did not continue the follow-up in the unit.

Subgroup of minor transsexuals (n = 53): 57% assigned female sex, average age at first visit 11.2 ± 3 (range 4-15) and distribution of pubertal development: 36% prepubertal, 19% Tanner II-III and 45% Tanner IV-V. Average age in the social transition was 11 ± 3 years (range 4-15). 83% made the social transition before attending the GIU. 51% received analogues of the gonadotropin-releasing hormone that began at 13.7 ± 2.1 years (range 9-16). 21% were on cross-hormone therapy initiated at 15.6 ± 2.1 years (range 14-16). The transsexual girls visited the GIU and made the social transition before the boys [visit by age: 10.1 ± 3.7 vs. 12.5 ± 2.5 , p=0.03; Age transition: 9.8 ± 3.6 vs. 12.1 ± 2.8 , p=0.01; Mann-Whitney test]

Conclusions: Assistance to transsexual adolescents is progressively increasing. Most of the children/adolescents made the social transition before attending the GIU. The transsexual girls consult and make the social transition earlier than boys. The percentage of children who have left the GIU is low.

46, XX and SRY FISH analysis was negative. Laparoscopy was performed to remove the labial mass, and for gonadal biopsy. The labial mass turned out to be a lipogranulomatous mass of no clinical significance. Uterus and Mullerian structures were observed in laparoscopy. The gonadal biopsy revealed bilateral ovotestes. The ovarian tissue included follicular cysts and testicular tissue showed the presence of seminiferous tubules with spermatogenesis. There was a clear demarcation between ovarian and testicular tissues in histological examination. The patient was started on oral contraceptive to induce menstrual bleeding, promote feminization and reduce serum testosterone levels. Further genetic analysis was negative for SF-1 gene mutations and SOX-9 duplications. The gonads were positive for Y chromosome markers including SRY, AZFa and AZFb establishing gonadal chimerism. The patient is currently being evaluated regarding the best surgical options to preserve future fertility.

Conclusions: 46, XX ovotesticular DSD is a very rare cause of virilization in a adolescent female. Gonadal chimerism should be considered in the etiology of 46, XX SRY (-) ovotesticular DSD.

P2-255

A rare cause of 46, XX ovotesticular DSD: Tetragametic gonadal chimerism

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Introduction: Virilization and hirsutism are clinical findings of androgen excess in females mostly due to polycystic ovary syndrome, although androgenic drugs, nonclassic congenital adrenal hyperplasia and androgen secreting adrenal/ovarian lesions are also implicated. 46, XX ovotesticular disorder of sex development (DSD) is the rarest form of DSD with an incidence of less than 1 in 20000.

Case Report: A 15-year-old adolescent girl was referred to the endocrine outpatient clinic due to apparent virilization. Physical examination was unremarkable except android habitus, hirsutism and cliteromegaly. Genital examination revealed a soft, ovoid mass in right labium with a longitudinal diameter of 2 cm. Pubertal staging was Tanner 4. Medial history revealed genital reconstruction due to ambiguous genitalia at 4 yr of age, with no subsequent follow-up. Her parents were first cousins. Initial laboratory work-up at admission was significant for elevated basal serum LH (24 mIU/L) and elevated serum total testosterone (1.4 ng/mL and 2.1 ng/mL). Standard ACTH test and DHEAS level was normal. Peripheral blood karyotype analysis (30 metaphase) was

P2-256

A Clinical and cytogenetic study of patients with Disorders of Sex Development (DSDs) Associated with Congenital Anomalies or Recognizable Syndromes

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Disorders of sex development (DSDs) represent a diverse group of clinical conditions which have a very wide phenotypic spectrum associated with a complicated molecular background. Such conditions are considered among the most common birth defects and are frequently associated with congenital abnormalities.

Herein we present 62 patients with DSD associated with somatic anomalies. Patients were selected from clinical genetics dept., NRC. They underwent complete clinical assessment, Quigley scoring of external genitalia and pubertal staging. Chromosomal analysis of the peripheral blood lymphocytes, using conventional GTG banding technique were done for all patients and FISH analysis was performed whenever indicated

8 patients had numerical sex chromosomal abnormalities; 2 had translocation of a sex chromosome to an autosome; 12 patients had different autosomal abnormalities; 25 patients had apparently normal 46,XY, of them six were clinically diagnosed with recognizable syndromal presentations; 15 patients had 46,XX karyotype, one of them was clinically diagnosed as having Rubinstein Taybi syndrome.

The study emphasizes the crucial need to improve the clinical utility of genetic analysis in patients with DSD. Improving the diagnostic strategy of such complicated disorders will be reflected on the patients and their families regarding possible therapeutic interventions, recurrence risk and carrier detection.

P2-257

Physical changes, laboratory parameters and bone mineral density during testosterone treatment in adolescents with gender dysphoria

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Introduction: Although many adolescents with gender dysphoria (GD) are being treated with GnRH analogues (GnRHa) and gender affirming hormones there is a paucity of data on the effects and side effects of this treatment in this population. We aimed to study short-term outcome of testosterone treatment in male adolescents with GD.

Methods: Sixty-two adolescents who had been treated with GnRHa, and subsequently with testosterone from a median age of 17.2 years (range 14.9-18.4) for a median duration of 12 months (range 5-33) were included. Physical changes and results from laboratory investigations and bone densitometry were assessed.

Results: In 85% of adolescents testosterone treatment led to a drop of voice and increased hair growth within three months. Acne was common and most prevalent at 6-12 months of treatment. BMI and systolic blood pressure increased. HDL-cholesterol and SHBG decreased whereas hematocrit, hemoglobin, prolactin, androstenedione and DHEAS increased. BMD z-scores after 12-24 months of testosterone treatment remained below z-scores before the start of GnRHa treatment.

Conclusion: Testosterone effectively induced virilisation starting within three months in the majority of adolescents. Acne was a common side effect but no short-term safety issues were observed. The increased hematocrit, decreased HDL-cholesterol and decreased BMD z-scores are in line with previous studies. Further follow-up studies will need to establish if these changes result in adverse cardiovascular outcome and increased fracture risk in the long term.

P2-258

Study of Autistic Features among children and adolescents with Congenital Adrenal Hyperplasia

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Introduction: Autism spectrum disorder (ASD) consists of a pattern of persistent deficits in social communication and interaction across multiple contexts together with restricted, repetitive

patterns of behavior, interests or activities. In the general population autistic traits can be found more frequently in males than females. This male predominance indicates that high androgen levels may prenatally have influence on development of autistic traits.

The 'extreme male brain' theory (EMB) states that exposure to high androgen levels during the critical window of fetal development gives rise to behavioral changes contributing to ASD.

Congenital Adrenal Hyperplasia (CAH) is an ideal way to study the influence of androgens on behavior in children after exposure to high testosterone levels in fetal development.

Aim of the Work: To study the occurrence of autistic features among children and adolescents diagnosed with CAH and to assess the relationship between levels of serum Testosterone and autistic features found among them.

Subjects and Methods: This study included 51 children and adolescents with CAH attending the endocrinology clinic in Alexandria University Children's Hospital, Egypt. Thorough history taking and clinical examination were done with emphasis on behavioral abnormalities pointing towards presence of autistic traits according to DSM-5 criteria. Severity rating scale for the ASD using CARS-2 scale was done. Total serum testosterone was measured.

Results: There were 36 females (70.6 %) and 15 males (29.4%). The mean age of the cases was 7.3 years; they had CAH with mean duration of 6.7 years. There were 4 cases (7.8%) still had elevated levels of serum Testosterone. According to CARS-2, 6 children (11.8%) showed mild autistic disorder, however all children were normal by DSM-5. Those children with mild autistic features were 3 males and 3 females, and only one of them still had elevated serum Testosterone.

Conclusion: Children with CAH may have more risk for autistic features so they have to be screened if they showed clinical suspicious behaviour.

P2-259

Differences of sex development with chromosomal mosaicism: histological characterization and immunohistochemistry markers in gonads during childhood

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Sex chromosome disorders, including sex chromosome mosaicism, result in a large clinical spectrum. There is scarce information about the histological pattern of these gonads.

Aim: to characterize the histology and cell markers pattern in gonads of patients with chromosomal mosaicism.

Gonadal biopsies from thirteen patients with chromosomal mosaicism, including chromosome Y were studied. Six were rearing as male and seven as female .

Patients were divided in two subgroups (G), according to external genitalia. G1, with atypical genitalia:n=7, chronological age(CA) at biopsy, was 1.75, 0.25-12 years(y) expressed as median and range. Five patients were rearing as males and two as females. G2, Turner syndrome,n=6,CA at biopsy was 13.8, 3.5-18.8 y, all patients were reared as females.

H&E sections from gonadal biopsies were observed by two specialists. Immunohistochemical studies for the detection of pluripotential marker OCT 3/4, Sertoli cell marker SOX9 and granulosa cell marker FOXL2 were done.

A total of 24 samples were studied, 13 from G1 and 11 from G2. Dysgenetic testicular parenchyma was found in 8/13 of G1 (62%) and 3/11 of G2 (27%). Only one sample with ovarian structures was found in G2. Histological structures compatible with streak were observed in 4/13 in G1(31%) and in 5/11(45%) in G2. Mullerian structures were found in 6/13 of G1(46%) and in 2/11(18%) in G2. In 4 samples of 2 patients gonadoblastoma, embryonic carcinoma and dysgerminoma were found, both corresponding to G2. Of the samples that presented testicular parenchyma, 43% had structures compatible with Mullerian remnants. OCT 3/4 was expressed in 42.8% of G1, all of them corresponding to testicular parenchyma, and in 66.7% of G2. All the patients were older than 3 months. SOX9 was present in 75% of G1, in the nucleus of Sertoli cells inside the seminiferous cords. Positive expression of SOX9 was found in isolated nuclei of tissues of G2(50%) without seminiferous cords. FOXL2 expression was found in 33.3 % of G1 and in 100% of G2.

In conclusion, the complexity of the tissues corresponding to patients with chromosomal mosaicism requires a deep histological and immunohistochemical analysis that allow the characterization of cell types and cell cancer risk. Samples of G1(2/7) showed testicular parenchyma and Mullerian remnants, which might indicate an early alteration in the function of the Sertoli cell. The expression of Sertoli cell marker SOX9 in streak tissues of G2, suggests an increased risk of gonadoblastoma development.

P2-260

Heterozygous CYP11A1 mutation associated with 46XY Disorder of Sexual Differentiation and mild Adrenal Insufficiency

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Background: CYP11A1 encodes the P450 side chain cleavage (scC) enzyme. This protein localises to the mitochondrial inner membrane and catalyses the conversion of cholesterol to pregnenolone which is the first and rate-limiting step in the synthesis of all steroid hormones. P450scC deficiency is a rare disorder that can present as adrenal insufficiency and varying degrees of disorder in sex development (DSD) in 46XY individuals. Typically, this disorder is caused by biallelic loss of function variants in CYP11A1, either homozygous or compound heterozygous mutations. We describe an infant with 46XY DSD and mild adrenal insufficiency associated with CYP11A1 heterozygous mutation.

Case: A pre-term infant (36/40) with a birth weight of 2.9kg born to non-consanguineous parents, presented on day 1 of life

with hypoglycaemia and concerns regarding DSD. Examination showed perineal hypospadias, chordee and cryptorchidism. The karyotype was 46 XY. An ultrasound of pelvis did not show Mullerian structures and demonstrated the presence of bilateral testes in the inguinal region. The plasma electrolytes remained stable. Investigations into the cause of hypoglycaemia showed an inappropriately raised plasma insulin level at the time of hypoglycaemia consistent with hyperinsulinism (HI). The 17 hydroxy progesterone, aldosterone, and renin levels were normal. A short synacthen test showed a suboptimal peak cortisol response of 397nmol/L. The hypoglycaemia was not persistent and completely resolved without specific medical interventions, suggestive of a transient HI picture.

Target sequence analysis of the genes implicated in 46 XY DSD identified a heterozygous frameshift mutation c.835delA p.(Ile279Tyrfs*1) in CYP11A1. This variant has previously been reported as pathogenic and in a recessive state has been shown to cause severe adrenal insufficiency and 46XY sex reversal. Heterozygous loss of function of CYP11A1 variants has been rarely reported to cause relatively mild clinical features due to haploinsufficiency. In the absence of other reasons for the mild adrenal insufficiency and undervirilisation seen in our patient, it is possible that the heterozygous CYP11A1 mutation (c.835delA p.(Ile279Tyrfs*1)) is contributing to the phenotype.

Conclusion: Recessive (homozygous and compound heterozygous) CYP11A1 mutations are known to result in severe adrenal insufficiency and DSD in 46XY infants. Heterozygous loss of function mutations in CYP11A1 can cause mild adrenal insufficiency and undervirilisation in 46XY infants as seen in our patient. However due to the rarity of such descriptions in the literature, more reported cases and molecular studies might add to the body of evidence.

P2-261

The Modern Approaches to Differential Diagnosis of Constitutional Delay of Puberty and Hypogonadotropic Hypogonadism in Boys

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Objective: We assessed the accuracy of the GnRH agonist test (Triptorelin 0,1 mg) and the human chorionic gonadotropin (hCG) test in comparison with basal sex hormones for the differential diagnosis of constitutional delay of puberty (CDP) and hypogonadotropic hypogonadism (HH) in boys.

Materials and Methods: The study included 56 boys with delayed puberty. The first medical visit was in the 14,5±0,9years. We evaluated LH, FSH, testosterone, anti-Mullerian hormone (AMH), inhibin B and the results of the stimulation tests. The HH was defined by a testicular volume <3cm³ after 2 years follow-up. The patients were divided into two groups: the first group with CDP and testicles ≥3cm³ (n=50) and the second group with HH and testicles <3cm³ (n=6). The second group of boys had additional

properties, they are often combine with HH: three boys- anosmia/hyposmia, one boy -defect of the gene Prop-1, one boy- micropenis and anosmia.

Results: At the first visit all patients had the same testosterone (Me 1,2 vs 0,9 nmol/l, p=0,2), AMH (Me 32,3 vs 23,4 pg/ml, p=0,1). However, at the first visit in boys with CDP, hormones were significantly higher, such as, LH (Me 1,1 vs 0,1 IU/ml, p=0,0002), FSH (Me 1,9 vs 0,2 IU/l, p=0,00007), inhibin B (Me 142,3 vs 31,3 pg/ml, p=0,00009), max LH (Me 18,9 vs 0,6 IU/ml, p=0,00007), maxLH/maxFSH (Me 2,3 vs 0,4, p=0,0002) on the GnRH agonist test and Δ testosterone (Me 14,4 vs 1,1 nmol/l, p=0,0001) on the hCG test than in boys with hypogonadotropic hypogonadism. The basal LH \geq 0,3 IU/ml had 86% sensitivity, 100% specificity (AUC0,935 \pm 0,034, 95% 0,869-1); maxLH/maxFSH \geq 1- 92% sensitivity, 100% specificity (AUC0,960 \pm 0,025, 95% 0,91-1); Δtestosterone \geq 2,7 nmol/l on the hCG test - 98% sensitivity, 100% specificity (AUC0,996 \pm 0,006, 95% 0,985-1) for differential diagnosis of CDP and HH in boys. However, max LH \geq 3,5 IU/ml on the GnRH agonist test, basal FSH \geq 0,5 IU/l, inhibin B \geq 58 pg/ml had 100% sensitivity and specificity (AUC1 \pm 0,95% 1-1).

Conclusion: The max LH \geq 3,5 IU/ml, maxLH/maxFSH \geq 1 on the GnRH agonist test and Δ testosterone \geq 2,7 nmol/l on the hCG test have an excellent accuracy for the differential diagnosis of CDP and HH in prepubertal boys with delayed puberty. However, basal LH \geq 0,3 IU/ml, basal FSH \geq 0,51 U/l, inhibin B \geq 58 pg/ml are a reliable and less-invasive alternative test.

6.75(64.7) months in SV-CAH and 1(3.63) months in SW-CAH. Phallus size was 34.3 \pm 17 mm in SV-CAH, and median 20(40) mm in SW-CAH. CYP21A2 mutations were detected in 26 patients with CAH. Two patients had CYP11B1 mutation. One patient had CYP19A1 mutation. Etiology was not found in two patients with clitoromegaly.

Feminizing genitoplasty was performed in four of six patients who were given male identity, and two of them were performed masculinizing genitoplasty. Clitoroplasty performed in 42.3% of patients with CAH. The age distribution of the clitoroplasty was examined: 0 - <12 months, four patients, 13 months-60 months, 26 patients, > 61 patients seven patients.

Patients with ovarian dysgenesis (OD, n:20) presented with delayed puberty (15.4 \pm 1.6 age old). Two sisters have homozygous mutation in HAX1 (p.TRp44X). They also have sensorineural hearing loss and OD. One patient diagnosed as ovotesticular DSD. His karyotype was 46,XX.

Admission age was 14.26 \pm 1.9 years in patients with Mayer-Rokitansky-Müller-Hauser syndrome (MRKHS, n:4). Renal agenesis, pelvic kidney, mitral insufficiency and aortic stenosis, coccyx agenesis and craniostenosis were detected in patients with MRKH Type 2.

Conclusion: The most common etiological diagnosis in 46 XX DSD was CAH due to intrauterine androgen exposure. However, this study showed that ovarian dysgenesis should also be considered in adolescents with puberty delay.

P2-262

Etiologic Classification of 46, XX Disorders of Sexual Differentiation According to Chicago Consensus: Single Center Results

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Objective: The aim of the study was to describe the etiologic diagnosis, clinical characteristics in children with 46,XX disorder of sexual development (DSD).

Methods: The 86 46, XY patients were included the retrospective study. The definitive diagnosis was made by presentations and clinical findings, gonadal morphology and genital anatomy of patients, basal and stimulated hormone results, imaging methods, molecular genetic analyzes and feminizing or masculinizing genitoplasty. All data obtain from hospital records.

Results: Types and ratios of each presentation of the 86 patients with 46,XX DSD were as follows. Majority of the patients were in androgen excess group (n:60, 69.7%). Patients with disorders of ovarian development were the second (n:21, 24.7%). Among the androgen excess group, salt-wasting congenital adrenal hyperplasia (SW-CAH) was the major group (55%), simple virilization-CAH (SV-CAH) was the second (40%). Parental consanguinity detected in %63.3 in SW-CAH and %54.5 in SV-CAH. Siblings of seven patients with SW-CAH and siblings of four patients with SV-CAH have same disease. At the admission, median age was

P2-263

Novel genotype in two siblings with 5-alpha-reductase 2 deficiency:different clinical course due to the time of diagnosis

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Background: Steroid 5-Alpha-Reductase-2 deficiency(5-ARD) is a result of mutations in the SRD5A2 gene. It causes disorder of sexual differentiation(DSD) in 46XY individuals with a variable genital phenotype. We present two siblings with a female external genitalia at birth and bilateral inguinal testes, raised as females. These are the first molecularly characterized patients from the Republic of Macedonia with a different clinical course due to the time of the diagnosis.

Case Presentation: Diagnosis of the Patient 1 was based upon the detection of bilateral inguinal testis and testosterone/dihydrotestosterone ratio. Sex reversal was initiated by testis removal at the age of 20 months. Breast implantation and vaginoplasty were performed in adolescence and the girl is comfortable with the female sex. Her sibling, Patient 2, raised as a girl, was clinically assessed at 11.5 years due to the growth of phalus, deep voice and Adam's apple enlargement.No change of the gender was accepted.

Complex molecular analysis including multiplex quantitative fluorescent PCR screening for sex chromosome aneuploidies and SRY presence, Sanger sequencing combined with MLPA, aCGH, and real-time PCR analysis for detection of exon copy number changes confirmed a novel c.146C>A(p.Ala49Asp) point mutation in the first exon inherited from the mother and complete deletion of the first exon and adjacent regions inherited from the father.

Conclusion: Novel genotype causing 5-ARD is presented. Genetic analysis is useful for the diagnosis and timely gender of patients with 5-Alpha-Reductase 2 deficiency. However, final gender assignment is difficult and requires combined medical interventions.

showed that a majority of CAH women thought that genitoplasty should occur within the first year of life. The dsd-LIFE study reported that only 0.5% of 46,XX CAH women had a gender change after puberty. Few case reports document the outcome of male gender assignment in severely virilized CAH girls. Our case highlights the dilemmas a team may encounter. The local ethics committee role was to give an external, unbiased view. Our experience shows the importance of assessing the parents' capacity to cope with their child's difference and the perception of society, while ensuring the most open and the least prejudicial decision for the child's psycho-sexual future. More research will be needed to base our recommendations on solid results from the DSD community, but every patient and his family will still need an individual approach and personalized care.

P2-264

Ethical and familial dilemmas of genitoplasty encountered in Congenital Adrenal Hyperplasia

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Differences of sex development (DSD) occur in about 1 in 3000 newborns in Switzerland. The indication and timing of genitoplasty in children with DSDs is a complex issue. In 2012 the Swiss National Advisory Commission on Biomedical Ethics published its position against early irreversible interventions in order to "normalize" the aspect of the external genitalia.

We report the case of a child with a 46,XX DSD due to a classical form of congenital adrenal hyperplasia (CAH) with severe virilization (Prader stage V). Direct DNA sequencing of *CYP21A2*, showed two maternal (IVS2-13A/C>G; p.Val281Leu) and one paternal mutation (p.Arg354Cys). The interdisciplinary team took care of the patient and the family according to the consensus statement on care of DSD individuals. In agreement with the parents, female gender was assigned and no surgery planned until the child could participate in the decision making. When the child was 3 years old, the parents informed the team that they had met a surgeon in their home country and that they planned genitoplasty in one month. The Clinical Ethics Committee of the hospital was convened to reflect on the situation. Despite their and our advice to postpone surgery the family decided to go forward with the surgery and left Switzerland.

Determining the best care and interests of this child remain a big challenge, and his future development unknown. Human rights organizations defend the children's right to physical integrity and to defer any normalizing interventions on genitalia until the concerned individual can give his consent. However, studies

P2-265

Hormonal assessment of malformation syndromes associated with disorders of sex development: Case series of 9 patients

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Introduction: Disorder of sex development (DSD) is a challenging condition confronting the patients, their relatives and the clinicians. It is more challenging when this disorder is associated with other extra-genital malformations. This makes their overall management more complex than if they just had DSD. Moreover, some of them have disturbed testicular function.

Aim of the Work: this work aimed at clinical review of 9 cases with malformation syndromes associated with DSD and evaluation of their testicular hormonal status.

Subjects and Methods: patients with syndromic DSD attending the Endocrinology clinic in Alexandria University Children's Hospital were assessed on emphasis on detailed history taking, thorough clinical examination (genital and extra-genital examination), reproductive hormonal assessment, karyotype analysis and the appropriate imaging study.

Results: Upon review of 9 cases with malformation syndromes associated with XY DSD, they had variable extra-genital manifestations such as steroid resistant nephritic syndrome, hypothyroidism, learning disabilities, skeletal anomalies, cardiac anomalies, renal anomalies and choanal atresia. Three patients were diagnosed as definite syndromes. Two cases had Robinow syndrome and one case had chromosome 13 q deletion syndrome. The remaining 6 patients having multiple malformations were not yet diagnosed as definite syndromes. Furthermore, these malformation syndromes were classified into two subtypes. The first group including 5 patients had abnormalities of hormonal function. In the second subtype, 4 patients have normal sex hormones but have a primary morphological defect of genital development. The first group included the two Robinow syndrome patients, two patients with gonadal dysgenesis and one patient with inadequate testosterone response after hCG stimulation. The second group patients had average testicular hormonal function either in mini-puberty or after hCG stimulation with normal T/DHT ratio.

Conclusion: Malformation syndromes with XY DSD are more challenging conditions either in work up to reach the definite diagnosis or in counseling for families about their affected children or other siblings. Even in syndromic XY DSD, there is a possibility of disordered testicular hormonal function that becomes overt in some patients. That highlights the importance of adequate hormonal assessment in all patients with XY DSD even those with other malformations.

P2-266

Family Perrault syndrome in two Tunisian sisters

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Introduction: Perrault syndrome (PS) is a rare disease characterized by a premature ovarian failure (with primary or secondary amenorrhea) and a sensorineural deafness. In this context we report the case of two sisters issuing from consanguineous parents presenting the association of these two anomalies.

Cases: The reason for consultation was primary amenorrhea in both cases at age 16 and 21 years respectively, on examination the assessment of their tanner stage was S1P2A2 and both girls also suffer from congenital deaf-mutism and a strictly normal clinical examination, in particular their neurological state because some neurological features are often described such as cerebral ataxia, neuropathy, mild development delay or oculomotor disorders in Perrault Syndrome. The hormonal exploration objectified a typical profile with hyper-gonadotropic hypogonadism and their karyotypes highlight a chromosomal formula compatible with gonadal dysgenesis 46 XX. The pelvic ultrasound confirms the absence of ovaries in both cases and the presence of a hypoplastic uterus. An additional medical imaging by cerebral magnetic resonance in the second daughter shows the presence of signs of cerebral leukodystrophy without clinical manifestations from where the interest a regular follow-up of the patient with neurologic examination and repeated audiograms could allow detecting precociously a deafness or neurologic troubles which could appear later on Perrault syndrome.

Conclusion: Perrault syndrome is a heterogeneous disorder, which is an agreement with different etiological mechanisms. And this syndrome is underestimated in adult patients. We suggest performing an audiogram to patients with unknown origin of premature ovarian failure, particularly in case of neurological features or history of familial sensorineural deafness.

P2-267

An intriguing co-occurrence of MURCS and VACTERL association: a case report and review of the literature

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Background: MURCS association is a rare developmental disorder that primarily affects the reproductive and urinary systems. MURCS is an acronym which stands for (M)Ullerian, (R)enal, (C)ervicothoracic (S)omite abnormalities. Males and females with MURCS association often have short stature and might suffer from hearing loss. MURCS anomalies are present at birth but may not be noticed until puberty, and then present as primary amenorrhea, or discovered incidentally because of abdominal pain or other complaints. VACTERL association refers also to a group of congenital defects that tend to co-occur. VACTERL stands for (V)ertebral defects, (A)nal atresia, (C)ardiac defects, (T)racheo-(E)sophageal fistula, (R)enal anomalies, and (L)imb abnormalities. Patients diagnosed with VACTERL association typically have at least three of these characteristic features. Some of the features of VACTERL association may not be identified until late in childhood or adulthood, making diagnosis of this condition difficult. The cause of MURCS and VACTERL association is unknown. There is no link to known teratogens and there is no known genetic cause discovered so far.

Patient and Methods: A 12 year old girl was referred for genetic counseling. She was born with tracheoesophageal fistula. Karyotyping was performed prenatally and was compatible with normal XX female. She had been under an endocrinologist's surveillance since the age of six years, because of short stature. Her physical examination demonstrated fusion of the labia minora which led to further imaging studies, including a pelvic ultra sound, pelvic MRI and a cervical X-ray.

Results: The patient underwent pelvic ultra sound which showed abnormal genitalia. MRI of the pelvis revealed a horseshoe kidney and vaginal atresia. A cervical x-ray was completed and demonstrated C6-7 blocked vertebrae.

Conclusion: MURCS and VACTERL associations have several defects in common, and yet they are considered distinct clinical entities. This patient follows the diagnostic features of both MURCS and VACTERL association. A co-occurrence of the two has been reported in only three case reports in the past and may imply to a common pathway leading to this unique phenotype. In cases of short stature, additional findings such as tracheoesophageal fistula or urogenital anomalies, should alert the clinician and result in further investigation. Future studies will possibly reveal the embryonal and genetic mechanism leading to these congenital defects, and will enable accurate genetic counseling regarding siblings and offspring.

P2-268

The Effect of Vitamin D Supplementation on Androgen Levels of Adolescent Girls with Hyperandrogenism

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Aim: The aim of this study was to evaluate the effect of different doses of vitamin D supplementation on androgen levels in adolescent girls who were treated with metformin.

Method: 45 adolescent girls diagnosed with hyperandrogenism were divided into the 3 different groups according to the treatment scheme. Patients treated with metformin (850 mg / day oral) (n = 15), metformin and vitamin D drops (2,000 IU / day) (n=15), metformin and vitamin D ampoule (150,000 IU / month) (n=15) were examined as group 1, group 2 and group 3, respectively. Biochemical and hormonal parameters were compared statistically after 8 weeks.

Results: There was a significant positive correlation between total testosterone and ALT in group 1 and group 3 ($p < 0.05$). There was a positive correlation between total testosterone and estradiol in group 1 and group3 ($p = 0.00$, $p = 0.01$, respectively). There was a positive correlation between SHBG and vitamin D and negative correlation between SHBG and androstenedione level in group 1. However, there were not any statistically significant difference between HOMA-IR ($p = 0.46$), total testosterone ($p = 0.61$), free testosterone ($p = 0.69$) and insulin ($p = 0.61$) over time.

Conclusion: Our study has shown that eight weeks' metformin and vitamin D supplementation did not have a positive effect on serum insulin levels, HOMA-IR, serum lipids, testosterone, androstenedione and DHEAS levels in adolescent girls with hyperandrogenism.

P2-269

Pseudo-precocious puberty in children triggered by incidental transdermal contamination with topical sex steroids through parents

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Introduction: Pseudo-precocious puberty may be triggered by either endogenous or exogenous sex steroids. Accidental ingestion of contraceptives, anabolic steroids or life style products containing sex steroids as well as transdermal transmission of topical sex steroids may cause early onset of secondary sexual development.

Objective: To report the clinical course of incidental contamination with topical sex steroids in children applied by their parents for replacement therapy.

Patients: Three patients (two girls and one boy) aged 6 months, 4.4 years and 4.9 years presented with signs of sexual precocity for further evaluation. One boy (4.4 years) and one girl (4.9 years)

presented with breast development in Tanner stage 2, which had been noted over a period of 1 to 6 months respectively. Both of the patients' mothers reported self-application of topical estradiol (spray and cream) for treatment of ovarian failure. The girl aged 6 months presented with premature pubarche and hyperpigmentation of the labia majora. Her father reported daily topical use of testosterone gel. Growth velocity was accelerated in all patients (SDS 5.14 ± 0.68). Bone age according to Greulich & Pyle was determined in 2 patients and found to be accelerated by 6 months in 6 month girl and by 2 years in 4.9 years girl. Serum concentrations of 17 β -estradiol in the girl (18.1ng/ml) and boy (25.6 ng/ml) presenting with thelarche and the total testosterone level in the girl (546 ng/dl) with premature pubarche were above the age and gender related references while serum gonadotropins were low and appropriate to age (LH<0.1U/L, FSH 2.1-5.8U/L). Awareness of possible transdermal contamination, improvement of hygiene, discontinuation of parental treatment or other method of application, reverted physical signs and laboratory findings of puberty in all children.

Conclusions: Incidental contamination by topical sex steroids from parental medication is a rare but potential cause of iso- or heterosexual pseudo-precocious puberty in children. Parents are unaware of the dangers of passive transfer. Therefore, patients need to be educated before starting treatment with topical sex steroids in order to avoid transdermal transmission of sex steroids to other family members with deleterious consequences. Discontinuation of contact resulted in a decrease of sex steroids levels and regression of symptoms.

P2-270

Follow-up of individuals with gender identity disorders: A long and challenging process

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Background/Aim: Gender identity disorder (GID) is a condition, which is characterized by incongruence between experienced gender and the natal-sex, which also causes deterioration of functionality. After psychiatric evaluations, medical treatment for adolescents with GID consists of 3 phases. First phase is the suppression of puberty with GnRH-analogues, which may be considered to be supporting the diagnostic process. In the second phase, cross-sex steroid hormones are added to GnRH analogues treatment. And the final phase is surgical procedures after the age of 18-years and keeping sex hormone levels in normal ranges. In our study, we aimed to raise awareness for individuals with GID, by presenting the clinical features and follow-ups of cases in our clinic.

Method: Twelve cases with GID included in this study who were referred between years 2016 and 2019 to our outpatient clinic for the necessary treatments during the gender transformation process. The complaints, clinical findings and follow-ups of these cases who received treatment were evaluated.

Results: Five cases were trans-female (MTF) and the remaining cases were trans-male (FTM). At the referral, the mean age was 16.6-years (min.13.3-max.21.6). Pubertal stage of one case was Tanner4, while the rest were Tanner5. All cases were uncomfortable by their natal-sex since early ages and their discomfort had increased especially during puberty. While seven of them were referred to our clinic by pediatric psychiatrists, the remaining five were brought by their parents regarding suspicions of hormonal disorders. Three trans-female cases had obesity, and hirsutism was detected in two of them. GnRH-analogue treatment (3.75mg/month) was started in five cases (3MTF, 2FTM) at a mean age of 17.2-years (min.16.7-max.17.6). In one case (MTF), the dose of GnRH analogue was required to be increased to 7.5mg/month. The induction of puberty was started in four cases (3 MTF, 1 FTM) at a mean age of 17.4-years (min.16.8-max.17.8). The trans-male case who was receiving cross-sex hormone, underwent mastectomy at the age of 17.7-years. Except one case, in which osteoporosis was detected during puberty suppression, no serious complications were observed.

Conclusion: The process of gender transformation in transgender individuals is a long and challenging journey. On the other hand, with a raised awareness it will be easier for these individuals to access appropriate and necessary treatments. With our increasing experience in our clinic, we are trying to assist these individuals medically and also supporting them on the way of increasing quality and satisfaction of their lives.

P2-271

Follow-up of two similar patients with Steroidogenic Factor-1 (SF-1/ NR5A1) variants, in two different eras

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Steroidogenic factor 1 (SF1)/“nuclear receptor subfamily 5 group A member 1” (NR5A1) is involved in adrenal and gonadal development, steroidogenesis and reproduction. The first patient, published in 1999 presented with a 46,XY difference of sex development (DSD) and adrenal insufficiency. The following year the first female patient with only adrenal insufficiency was described. Since then, heterozygous changes in SF-1/NR5A1 causing 46,XY DSD were found to be very frequent, while adrenal insufficiency is rare. Furthermore, SF1 variants are responsible for premature ovarian failure and ovotesticular DSD, suggesting a pivotal role in the development of both sexes.

Case studies: Patient 1(*1993) presented with ambiguous genitalia (phallus 1 cm), descended gonads and 46, XY karyotype. No salt wasting crisis. HCG test showed no increase of testosterone. Ultrasound revealed no uterus or vagina. At 3 years of age gonadectomy and clitoroplasty were performed. Histology showed immature seminiferous tubules with normal Sertoli cells. The patient was raised as girl. Vaginoplasty was performed at the age of 16. Psychosocial development was normal with achievement of high degree of education.

Whole Exome Sequencing showed a heterozygote novel variant in NR5A1/SF1 (c.64G>A p.(Gly22Ser)), and is compatible with a *de novo* event (Minor Allele Frequency, MAF=0).

Patient 2(*2016) presented with penoscrotal hypospadias (phallus 2.1 cm), at ultrasound the right testis in the scrotum and the left retained in scrotal/inguinal position. No adrenal insufficiency. Karyotype was 46,XY. Urine analysis suggested a testosterone synthesis defect. Testosterone injections at the age of 3, 4 and 5 months resulted in penis growth up to 3 cm. In the first year of life surgical correction of the hypospadias was performed. The patient's sex was assigned male.

Genetic studies showed a *de novo* heterozygote variant in NR5A1/SF1 (c.250C>T p.Arg84Cys), which has previously been reported to cause 46,XY DSD.

Conclusions: The novel p.Gly22Ser/WT in patient 1 and the c.250C>T p.Arg84Cys/WT in patient 2 are the most likely genetic cause of 46,XY DSD in our patients, given the dominant negative effect of SF1 variants.

These two cases emphasize the different management of two only slightly different phenotypes in patients with NR5A1/SF1 variants. Time of diagnosis (one patient born in 1993 and one in 2016) before and after the change of policy in management of DSD cases with the advent of multidisciplinary teams had probably a stronger influence on decision making for medical and surgical treatment and gender assignment than the phenotype.

P2-272

Genetic testing of DSD patients in Ukraine

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Background: In this study we investigated the genetic aetiology of a series patients with DSD seen in Ukraine.

Materials and Methods: The Ukraine Pediatric DSD Register has 95 children with DSD between the ages of 0-18 y.o. in 2018 (a prevalence of 1 in 80097). The criterion for including patients to the database was ambiguous genitalia and/or a discrepancy between the chromosomal and gonadal/genital sex. All patients had a karyotype performed and, if necessary, fluorescence in situ hybridization (FISH). We studied 30 probands with 46,XX or XY DSD for further exome sequencing studies.

Results and Discussion: Sex chromosome DSD was diagnosed in 17.9% (n=17), 46, XY DSD in 68.4% (n=65), 46,XX DSD in 13.7% cases (n=13). The most frequent variant of the karyotype among the first group was 45,X/46,XY (n=6; 35.2%). In a group of patients with 46,XX DSD we diagnosed: testicular 46,XX DSD (n=5), 21-hydroxylase deficiency with virilization IV-V degree by Prader (n=4), 46,XX gonadal dysgenesis (n=3) and DSD in VACTER-association (n=1). 3 patients were SRY positive. In a group of patients with 46,XY DSD 40 patients (61.5%) were registered in female sex, 25 patients (38.5%) as males. However in 46,XX group 8 patients (61.5%) were registered as males.

Genetic testing in 46,XY/XX DSD group was done in 30 (38.4%) cases. We determined the genetic etiology in 18 of 30 (60%) probands diagnosed with DSD. We report that AR (n=5) and NR5A1 (n=4) mutations are the commonest cause of 46,XY DSD in Ukraine, accounting for 30% of cases. Other genetic causes of 46, XY DSD included MYRF (n=2), WT1, SRD5A2, HSD17B3, DHX37, AMHR2, KAL and CBX2 variants. In 7 patients (23.3%) we found VUS variants and their causality should be proven in further studies. A multi-disciplinary team has been created for gender assignment in DSD newborns and to improve the decisions of further clinical management, including the time of gonadectomy.

Conclusions: Genomic analysis found a genetic cause in the majority of cases. Further studies to identify novel genes causing DSD are required.

P2-273

Spectrum of genital abnormalities in Robinow syndrome: Case series

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Introduction: Robinow syndrome is a rare genetic disorder characterized by mesomelic dwarfism, characteristic facial features, skeletal abnormalities and external genital abnormalities. Genital abnormalities may be noted in these patients and may cause confusion in gender assignment. In males, the characteristic pattern is micropenis with or without cryptorchidism, webbed penis or hypoplastic scrotum. In females, the anatomical defect is not always evident. There is hypoplastic clitoris and labia minora.

Aim of the Study: This work aimed at defining the genital abnormalities in 11 patients with Robinow syndrome following up in Alexandria University Children's Hospital.

Subjects and Methods: Eleven patients having Robinow syndrome were subjected to full history taking, detailed clinical examination and anthropometric measurements including height, weight, and head circumference. Furthermore, parents and available siblings were examined. X-ray studies, echocardiography, and chromosomal analysis, done by G-banding technique using peripheral blood sample, were performed for these patients.

Results: The study included 11 patients with Robinow syndrome. They included 7 boys and 4 girls. Their age ranged from 3 months to 66 months. History of consanguinity was found in 63.6% of these patients. Two patients had history of similar condition in their families. All of them had mesomelic short stature and the characteristic facial features. Five cases had cardiac anomalies.

Limbs anomalies such as clinodactyly, polydactyly, syndactyly and simian crease were observed in some of them. As regard genital abnormalities, all girls had no genital abnormalities. However, 90.9% of boys had genital abnormalities. Hypospadias was observed in 18.2% of boys, micropenis in 18.2%, cryptorchidism in 18.2% and hypoplastic scrotum in 18.2% of them. These anomalies were found either isolated or in combination in the form of disorder of sex development.

Conclusion: Robinow syndrome is diagnosed based on clinical and radiological findings. Genital abnormalities were very evident among male population in our cohort. These abnormalities include hypospadias, micropenis, hypoplastic scrotum, cryptorchidism or ambiguous genitalia.

P2-274

MAMLD 1 gene mutation and 46 XY sex development disorder : a case report

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Introduction: 46 XY sex development disorders are a group of rare congenital conditions in which chromosomal, gonadal or anatomic sex is atypical. Less than 20% of cases have a precise genetic diagnosis.

We report here the case of a patient suffering from a 46 XY sexual development disorder secondary to the MAMLD 1 gene mutation.

Observation: The patient is a nine month infant who was admitted for abnormalities of the external genital organs. The physical examination, revealed a 1.5 cm micropenis with posterior hypospadias, and normal positioned gonads. Blood karyotype showed 46 XY chromosome formula with a positive SRY gene.

Exocrine testicular function was found to be normal with an AMH level of 236.9 ng/ml, while endocrine function assessments are planned. The genetic study revealed a new mutation of the MAMLD 1 gene (c.G 2217 A:p.W739X). The patient has benefited from a cure of hypospadias and bifurcated scrotum, as well as several courses of medical micropenis therapy (cutaneous dihydrotosterone treatment).

Discussion: The MAMLD 1 gene is located at the position 28 of the long arm of the X chromosome.

This gene's mutation is responsible for the fetal Leydig cells function alteration during the critical period of sexual development. At birth, it leads to a 46 XY sexual development disorder. Therefore, testicular function is most often conserved during infancy, but it needs surveillance as it may deteriorate in long term.

P2-275

46,XY complete gonadal dysgenesis in a familial case with a rare mutation in the *Desert Hedgehog (DHH)* gene

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Purpose: Disorders of sex development (DSD) have been linked with gene defects that lead to gonadal dysgenesis. Herein, we aimed at identifying the genetic cause of gonadal dysgenesis in a patient with primary amenorrhoea and 46,XY karyotype from a consanguineous family.

Methods and Results: Whole exome sequencing (WES) was performed and revealed in homozygosity the rare and only once reported p.Arg164Pro missense mutation in exon 2 of the *desert hedgehog (DHH)* gene. Sanger sequencing was used to validate this candidate variant both in the patient, the parents and two other siblings. Both brother and sister of the index patient were found negative for the p.Arg164Pro mutation while the consanguineous parents were found to carry the mutation in the heterozygous state. Both the parents and the unaffected siblings showed no reproductive malformations.

Conclusions: Defects in the *desert hedgehog (DHH)* gene have been reported as a very rare cause of DSD and this report increases the number of 46,XY gonadal dysgenesis cases. Additionally, the present study highlights the importance of genetic validation of patients with DSD since might alleviate considerable psychological distress both in the patient and the parents.

Thyroid

P2-276

Novel thyroid hormone receptor β-gene mutations in resistance to thyroid hormone

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The syndrome of resistance to thyroid hormone (RTH) is caused by decreased tissue responsiveness to thyroid hormone. With the exception, inheritance of RTH is autosomal dominant. The receptors are encoded by two genes (*THRA* and *THRβ*), each of which undergoes alternate splicing to generate receptor subtypes (*TRα1*, *TRβ1*, and *TRβ2*), with differing tissue distributions. Here we describe a child with novel heterozygous mutations for *THRβ*. Nine-months-old boy presented with hyperthyroxinemia with inappropriately increased TSH levels. He had been treated with l-thyroxine under the diagnosis of congenital hypothyroidism before visiting our clinics. Goiter, growth retardation, delayed bone age, and tachycardia were absent. Alpha-subunit of thyroid hormone receptor was not elevated and TSH-secreting tumor was not found in brain MRI. TSH response to TRH test was exaggerated. Serum sex hormone binding globulin level was normal. Thyroid ultrasonography found no abnormality. Under the suspicion of RTH, targeted exome sequencing identified novel heterozygous mutations in *THRβ* (c.993T>G). The mutation was not found in parents. L-thyroxine was given to patients to maintain TSH levels < 5 mIU/mL. Further studies are required to obtain long-term data on RTH.

P2-277

Congenital Hypothyroidism: neonatal screening program with T4 and TSH

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Objectives: -To determine children diagnosed with central congenital hypothyroidism (CCH) by a screening program using TSH and total T4 between May 2016 and January 2019.

-To analyze the characteristics of the disease in these children.

Material and Methods: During the time of the study, 14.743 newborns have been screened. Cut-off points are used for TSH $\geq 10\text{MU/ml}$ and T4 6 and 20 mg/dl as lower and upper limits.

When the result was positive, a second sample was performed on filter paper and if the second sample was also positive, the patient was sent to the Pediatric Endocrinology Unit to confirm the results. Diagnosed of CCH was made with the combination of low FT4 and inappropriate low TSH. If the patient was diagnosed with CCH, hormonal studies, skull MRI and genetic analyses were performed.

Results: For total T4 values, first simple screening was positive in 112 patients (0'76% of total). Of these cases, the second sample continued to be positive in 17 cases (0'11% of the total), in which 10 the diagnosis was confirmed.

There were 2 cases with alterations of total T4 above the limit due to a resistance to thyroid hormones and another by insensitivity of thyroid hormones. The other 8 cases, had total T4 below the limit, being 2 hipothyroxinemas of the prematurity and 6 CCH.

There were 6 cases diagnosed of CCH and all were male. The incidence of HCC was 1/2500. In the screening, TSH was $1'5 \pm 0,61$ mU/l and Total T $1'89 \pm 0,25$ ug/dl; In the confirmation TSH was $2.44 \pm 1,36$ mU/l and FT4 $0'79 \pm 0,07$ ng/dl. Treatment was initiated with a medium age of $9'4 \pm 1,82$ days (except one case with 5 months) with L-thyroxin at a medium dose of 7 mcg/K/d. None of them had symptoms of hypothyroidism. At present, all continue treatment at a medium dose of 3 mcg/k/d. None of the patients have their TSH undetectable. In all patients the study of the pituitary hormones have been normal, and the MRI of the skull showed hypoplastic adenohypophysis in 3 cases. Genetic analysis of all genes known to be involved in central congenital hypothyroidism (IGSF1, TRHR, TSHB, TBLX1..) are under investigation.

Conclusions: -The analysis of TSH and total T4 in neonatal screening makes it more accurate the diagnosis of thyroid dysfunction.

-CCH represents a challenging condition in clinical practise

-The prevalence of HCC in our community is high, not being able to know the cause, although the genetic study can help with the diagnosis

P2-278

A 10- year-old girl with thyroid hormone resistance (β THR)- case report

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Introduction: Thyroid hormone resistance (THR) is a rare syndrome which is characterized by reduced response to thyroid hormones at tissue level. The disorder is caused by genetic mutation in the thyroid hormone receptor. The most common are a heterozygous thyroid hormone β (THR β) gene mutations. Laboratory tests usually show normal or elevated level of thyroid-stimulating hormone (TSH) and high concentration of thyroid hormones (T3 and T4).

Case Report: We present a case of a 10-year-old girl with signs of hyperthyroidism and abnormal thyroid function tests who was hospitalized in Department of Pediatrics, Endocrinology, Diabetology with a Cardiology Division, Medical University of Białystok. Her physical examination had revealed café au lait spot on abdomen skin, goiter, vascular murmur louder above right lobe of thyroid, tachycardia and heart murmur. In laboratory tests we found elevated serum levels of thyroid hormones: fT3- 14,55 pg/ml (norm: 2,7- 5,2) and fT4- 4,95 ng/dl (norm: 1,1- 1,7 ng/dl) co-existed with normal concentration of TSH -3,64 uIU/l. The thyroid autoantibodies were negative. In TRH stimulating test TSH concentration increased after TRH administration. Sonography revealed normoechogenic, asymmetric (right lobe bigger than left) thyroid gland with hypoechoic 5 x 4 mm area in left lobe, vascular flow was slightly increased in down parts of both lobes. Thin needle aspiration biopsy was performed. Result was benign.

Magnetic resonance imaging (MRI) showed normal pituitary gland and excluded pituitary adenoma. The diagnosis has been confirmed by next-generation sequencing, which exposed a pathogenic variant c.1034G>A in one copy of THR gene. The mutation is known and associated with THR.

Previously patient was given Magnesium, Vitamin D, Vitamin B complex and Propranolol at a dose 10 mg three times a day, which was changed into 20 mg three times a day. She is currently stable on this medication.

Conclusions: Although thyroid hormone resistance is rare, this disorder should be considered in patients with clinical manifestation and thyroid laboratory tests suggested its presence. Mutations of TR β gene can be seen in various clinical presentations, from isolated biochemical thyroid function abnormalities to thyrotoxicosis or hypothyroidism symptoms. The patients need individualised management.

P2-279

Diagnosis of central congenital hypothyroidism and multiple pituitary deficiencies through a neonatal screening program

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The congenital central hypothyroidism (CCH) incidence is estimated at 1:18,000-30,000 neonates and most are included in multiple pituitary deficiencies (MPD). Clinical depend on the etiology, the deficit severity; other associated hormonal alterations and the age of diagnosis. Neonatal screening (NS) for congenital hypothyroidism that includes T4 facilitate its diagnosis.

Objetives:

- To evaluate the characteristics of patients with CCH in the Basque Country.
- To evaluate the success of T4 in our NS for the early diagnosis of MPD.

Material and Methods: Retrospective study of 20 CCH controlled by pediatric endocrinologists of the Basque Country in the last 21 years [1997-2009: 426,174 live newborns]. The results of the NS performed at 48 hours of life, including T4 and TSH on filter paper, as well as clinical, hormonal and image data have been collected. The lower cut-off point for T4 in NS is 6 µg/dL. The patients were classified into 3 subgroups according to [T4]:<6 µg/dL (n=4), 6-8 µg/dL (n=8) and >8 µg/dL (n=6). MPD was diagnosed with affection ≥2 hormonal axes. Adrenal insufficiency (AI) detected in the first year of life was considered determinant of severity. Two cases without T4 levels were excluded.

Results: The CCH incidence is 1/22,308 live newborns. All patients (61% males) had MPD and pituitary malformation; The mean gestational age was 39 weeks (range:33-41) and the mean birth weight 3,175 g (range:2,300-4,100). 11/18 patients had AI and their average [T4] in NS was lower [AI:6±2.8 µg/dL versus non-AI:8.9±3.5 µg/dL; U-Mann-Whitney p=0.03].

Four patients had [T4]<6 µg/dL in NS. Three of them were diagnosed of AI in the first month of life but the fourth maintains adrenal function at 5 years. 7/8 of patients with [T4] between 6-8 µg/dL were diagnosed of AI before 12 months of age, associating clinical symptoms, alterations of the pituitary and/or other hormonal deficits. Only 1/6 of patients with [T4]>8 µg/dL was diagnosed with AI.

Conclusions:

1. The determination of T4 in the NS allowed an early diagnosis of 25% of the CCH, as well as the suspicion of MPDs.
2. Most of the MPDs including AI were diagnosed in the first year of life. In all of them, the [T4] in the NS was ≤8 µg/dL. Just considering a clinical point of view, we think it could be interesting to increase the lower cut-off of T4 in our NS.

P2-280**Childhood Thyroid Cancer after Radi Oiodine Therapy**

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Introduction: Differentiated thyroid cancer (DTC) is a rare disease in children and adolescents, it concerns approximatively 1.4% of all pediatric malignancies. Papillary thyroid carcinoma (PTC) is the most common subtype of DTC in pediatric as well as in adult with necessity of radio iodine therapy after surgery.

Aim : The aim of our study is to evaluate follow up after iodine therapy in childhood patients treated for PTC.

Materials and Methods: A cohorte of children with PTC diagnosis were follow up in our clinic after surgery and for more than 03 years after the first radio iodine therapy, they were assessed with clinical examination, biochemical and radiologic assessemnt.

Results: 20 children (07 Boys and 13 girls) with age rang between 06 to 16 years, with no history of exposure to external irradiations, 15 children underwent total thyroidectomy once a time and 05 went through twice time surgery. Lymphnodes surgery was performed in 13cases. Radio iodine therapy with 1,8 to 3,7 GigaBq were administrate in once a time for 08 children, in two times for 03 cases, and more than three times in 09 patients.

The post therapeutic scan showed iodine uptake outside the thyroid bed in 15% of the patients (lung metastases) while 85% had uptake only in the thyroid bed.

In our study 12 patients have an excellent response with indetectable thyroglobuline after more than five years of follow, whereas 05 patients have biochemical incomplete response and 03 patients present recurrence disease.

Conclusion: We conclude that young patients with DTC have a more aggressive clinical presentation with more frequent lymph node and distant metastasis comparing to what is usually seen in adults. The patients treated with high activities of radioactive iodine, especially children cases, should be carefully followed up during their whole lifespan.

P2-281**Differential diagnosis of euthyroid hyperthyroxinemia**

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Introduction: The pathology of thyroid gland in Ukraine is quite common and in 2018y included 277,708 patients with diffuse goiter (36.47 per 1000 population), 2,311 patients (0.30:1000) with nodular goiter, 341 patients with diffuse toxic goiter (0.04:1000), 7,157 (0.94:1000) with autoimmune thyroid disease and 129 patients with thyroid cancer (1.7:100000). However the syndrome of resistance to thyroid hormone (RTH) or Familial Dysalbuminemic Hyperthyroxinemia (FDH) are relatively uncommon disorders and have not been previously diagnosed.

Case presentation 1: A 5.5y.o. girl presented to endocrinologist with complaints on emotional lability symptoms and hyperactivity disorder. Diffuse euthyroid goiter was diagnosed, and she received iodine supplements within 6 months without improvement of her condition. Hereafter fT4 was measured, and raised level (5.7 ng/dl [normal range, 0.6-1.1]) was revealed on a background of normal TSH. Iodine supplements were cancelled and after 2 months repeated measurements of fT4 and fT3 showed their permanent increased levels (ranged 1.4-2.4 ng/dl and 5.1-6.2 pg/ml [normal range, 2.5-3.9], accordingly) on a background of normal TSH and negative TSH-receptor antibodies (TRAb), Ab-TPO and Ab-TTG levels. Detailed evaluation revealed similar changes of thyroid function tests in father (normal TSH level, increased fT4 and fT3 levels (2.9 ng/ml and 7.4 pg/ml accordingly), however no changes

in mother's and sister's tests. Subsequent genetic analysis of the patient and family confirmed RTH with *THR*B p.Arg438Cys, c.1312C>T variant in the proband and his father.

Case Presentation 2: A 13.4 y.o. Caucasian boy presented to endocrinologist with complaints of growth retardation since 2 years of age. According to the results of examination his height was 140 cm (-2.4 SD), repeated hormonal test revealed a constantly elevated level of fT4 1.65-2.14 ng/ml [normal range, 0.7-1.46], T4 14.9 mcg/dl [normal range, 6.4-13.4], fT3 4.15-5.16 ng/ml [normal range, 2.4-3.9] on a background of normal TSH, Ab-TPO, Ab-TTG and TRAb. Detailed examination showed similar changes of thyroid function in his father (elevated fT4 [1.73 ng/ml], and normal TSH, fT3 and T4). Clonidin test and measurement of IGF-1 level didn't confirm GH-deficiency in the child. Subsequent genetic analysis of the patient and his parents confirmed FDH with *ALB* p. Arg218His, c.725 G>A variant in the proband and his father.

Conclusion: Patients with euthyroid hyperthyroxinemia should undergo genetic testing due to the similar clinical presentation of RTH and FDH syndromes.

P2-282

Treatment for Graves' Disease in Children and adolescents: A Long-Term Retrospective Study at a Single Institution

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Background: Management options are limited for the treatment of Graves' disease (GD) in children and adolescents. Anti-thyroid drugs (ATDs) remain the first-line therapy in patients with GD, despite a high relapse rate. We investigated the clinical characteristics, treatment, the outcome, and predictors of a remission of children and adolescents with GD at a single center.

Methods: We retrospectively reviewed the medical charts of patients with GD diagnosed before 19 years old at Samsung Medical Center over a 7-year period (May 2011 to June 2018). Diagnostic criteria included clinical signs suggestive of GD, elevated free T4 and total T3, suppressed TSH, and positive thyroid receptor antibodies. Remission was defined as maintenance of euthyroid status for more than 6 months after discontinuing ATD.

Results: A total of 107 children and adolescents with GD were included in this study. Their median age (\pm standard deviation) at diagnosis was 13.5 years (range: 2.7–18.7 years), and 88 patients were females. All patients started to receive treatment with ATD at the time of diagnosis. Of the 107 patients, 23 patients (21.5%) achieved a remission, 78 patients (73.8%) continued to take ATD, 4 patients (3.7%) underwent surgery, and 2 patients (1.9%) underwent radioactive iodine (RAI) therapy. The median time to relapse after discontinuation after ATD was 4.0 months (range: 1.0–72.0 months) and the median time to remission in 23 patients who achieved a remission with ATD treatment was 28.2 months (range: 1.2–94.6 months). The cumulative remission rate was 5.2%, 23.3% and 37.0% within 1 year, 3 year and 5 year, respectively. Of the

107 patients treated with methimazole (MMZ), 10 patients experienced mild adverse reactions (AEs), and one patient experienced severe AEs. Higher serological titer of TSH-receptor-Ab at diagnosis was associated with lower remission rates ($p=0.017$).

Conclusion: Most children and adolescents with GD reach to euthyroid status with ATD treatment, however, more than 40% of patients who have attempted to discontinue ATD experienced one or more relapses. The overall incidences of AEs associated with MMZ were 9.3 %, and most of them were mild. Higher serological titer of TSH-receptor-Ab at diagnosis is considered as a predictor of lower remission rates. Long-term ATD treatment is a useful treatment option for most children and adolescents, however, other treatment options should be carefully considered in rare cases.

Keywords: Graves' disease, hyperthyroidism, Antithyroid drugs, Predictors of remission

P2-283

Changes of thyroid function in girls with central precocious puberty after 6-month GnRH agonist treatment

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Objectives: In our previous study, serum thyroid stimulating hormone (TSH) level in the central precocious puberty (CPP) group was higher than that of the non-CPP group. Serum free thyroxine (fT4) level in the CPP group was notably lower than that of the non-CPP group. And it was also showed that age and peak luteinizing hormone (LH) were independent predictors of serum TSH concentration. Elevated TSH in girls with CPP is supposed to be associated with pubertal LH elevation. But, the causal relationship between serum TSH and LH in girls with CPP has been unknown. The aim of this study was to evaluate the causal relationship between serum TSH and LH levels in girls with CPP treated with gonadotropin-releasing hormone (GnRH) agonist.

Methods: This is a prospective longitudinal study. A total 68 girls aged 6-9 years with CPP who were treated with GnRH agonist for 6 months. Hyperthyrotropinemia was defined as elevated TSH with normal fT4 (TSH \geq 5.0 mIU/L and fT4 \geq 0.8 ng/dL). Characteristic and laboratory data between before GnRH agonist treatment and after 6-month GnRH agonist treatment were compared.

Results: TSH, GnRH stimulated peak LH and FSH were significantly decreased after 6-month GnRH agonist treatment. Age, height and weight were significantly increased after GnRH agonist treatment for 6 months. There were no significant changes in body mass index, bone age and fT4 after GnRH agonist treatment for 6 months. All subjects except three subjects showed peak LH suppression (peak LH $<$ 3 IU/L) after GnRH agonist treatment. Across all subjects, 5 girls (7.4%) had hyperthyrotropinemia before GnRH agonist treatment. After GnRH agonist treatment, no subject showed hyperthyrotropinemia.

Conclusion: TSH elevation and hyperthyrotropinemia in girls with CPP are supposed due to premature LH elevation. Further large-scaled longitudinal studies are needed to confirm our results.

P2-284**Papillary Thyroid Cancer Associated With Hyperthyroidism**

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Introduction: The most common causes of hyperthyroidism in the pediatric age group are autoimmune conditions (Graves' disease or Hashitoxicosis). Hyperfunctioning thyroid carcinomas are rarely reported. In this case report, we present a 17-year-old girl who was diagnosed with papillary thyroid carcinoma upon testing for hyperthyroidism.

Case: A 17-year-old girl had presented to another center with a 1-month history of palpitations, hand tremors, and weight loss and was treated for 1 month with methimazole (5 mg twice a day) for a diagnosis of hyperthyroidism. Her history did not include any exposure to radiotherapy. There was no consanguineous marriage in her family history, but a cousin had undergone surgery for papillary thyroid carcinoma (PTC). On physical examination, her weight was at 1.66 standard deviation score (SDS), height 0.7 SDS, BMI 2.0 SDS. Pulse rate was 102/min and blood pressure 160/70 mmHg. Laboratory findings were as follows: fT4: 1.55 ng/dL (N, 0.50–1.51), fT3: 5.11 pg/mL (N, 2.5–3.9), TSH <0.015 µIU/mL (N, 0.38–5.33), anti-TPO: 0.5 IU/mL (N, 0–9), anti-TG: 0.9 IU/mL (N, 0–4), and TRAB <0.10 ng/mL (N, <0.10). Thyroid ultrasonography (USG) revealed homogeneous parenchyma with a 1.2-cm isoechoic solid nodule in the inferior left lobe; thyroid scintigraphy showed increased and homogeneous activity distribution in both lobes. Because the patient was symptomatic (tachycardia), her treatment was adjusted (methimazole 10 mg twice a day) and propranolol 40 mg twice a day was added. During clinical follow-up, an increase of over 20% in control thyroid nodule diameter was observed. Fine-needle aspiration biopsy (FNAB) revealed cellular crowding with atypia, and total thyroidectomy was performed for suspected PTC. The results of histopathologic examination were consistent with PTC. The patient tested negative for autoimmune markers and no mutation was detected in TSH receptor gene mutation analysis. There were no signs of vascular invasion on histopathologic examination, so radioactive iodine therapy was not planned. The patient is now euthyroid with L-thyroxine therapy (150 µg/day) and is continuing clinical follow-up.

Conclusion: Both pediatric and adult thyroid cancer patients are usually euthyroid. In the literature, the coexistence of thyroid cancer and hyperthyroidism has been reported at rates of 5–15%

in adult series. Hyperthyroidism associated with pediatric thyroid cancers has only been described in case reports. Functional thyroid malignancies should be included in the differential diagnosis for patients presenting with non-autoimmune hyperthyroidism and thyroid nodules

P2-285**Serum PTH does not correlate with their serum calcium levels in children and adolescents with Hashimoto thyroiditis**

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Background: Hashimoto thyroiditis (HT) is characterized by autoimmune-mediated destruction of the thyroid gland. Ca metabolism disturbance due to hypoparathyroidism among HT patients remains to be clarified.

Objective: To clarify the relationship between HT and primary hypoparathyroidism.

Patients and Methods: Serum levels of Ca, albumin, and whole PTH (wPTH, ECLIA) were measured in 21 patients with HT (mean age 13.4 years) and 18 thyroid autoantibody negative patients with type 1 diabetes as a control group (mean 15.0 years). Pearson's correlation coefficient was calculated for wPTH and albumin-corrected Ca value.

Results: In HT patients, the mean wPTH and corrected Ca were 28.39 pg/mL and 8.68 mg/dL, respectively. In the control group, the averages of wPTH and corrected Ca were 27.85 pg/mL and 9.03 mg/dL, respectively. There was a correlation between the wPTH and Ca levels in the control group with a correlation coefficient of $r = 0.497$ ($p < 0.05$), whereas no significant correlation was observed in patients with HT ($p = 0.190$). Even when excluding a patient with apparent hypocalcemia on treatment from the analysis, wPTH levels did not correlate with corrected Ca ($p = 0.079$).

Discussion: Serum PTH is strictly controlled by ionized Ca levels, though in this study, no correlation was found between PTH and serum Ca in patients with HT, which would indicate that PTH secretion is abnormal in patients with HT. Indeed, serum PTH was inappropriately low in one patient requiring treatment for hypocalcemia. In some cases of primary hypoparathyroidism, an autoimmunity to Ca-sensing receptor have been reported, so any autoimmune mechanisms to parathyroid may be suggested in HT patients.

Conclusion: We showed that some patients with HT might be suffered from low PTH secretion. It would be worth noting that hypocalcemia might be seen during the course of chronic thyroiditis.

P2-286**Management of childhood thyroid nodules in children a large group of cases from a single center**

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Background: Thyroid nodules are quite common in the adult population (13%) but are relatively rarely diagnosed in childhood (0.2–5%). There is a significantly higher risk of malignancy of paediatric thyroid nodules than that in adult patients. The authors of this publication present the observations of the occurrence, diagnosis, and treatment of patients with thyroid nodules in the Department of Pediatric Endocrinology and Diabetology, Medical University of Lublin, Poland.

Patients and Methods: We reviewed charts of patients diagnosed with thyroid nodules between March 2010 and December 2018.

Result: We retrospectively investigated 67 children (49 females and 18 males) diagnosed with thyroid nodule in our centre. 29 children (43.28%) with high risk for DTC (differentiated thyroid cancer) underwent surgery and were labelled as a high-risk group. 38 children (56.72%) with low risk for DTC were observed without surgical intervention and referred to as a low-risk group.

The mean age of all patients was 12 years 10 months (7 months - 18 years), the gender proportions in both groups were similar.

Visible or palpable swelling in the neck was the presenting symptom on admission in 56 patients (83.58%). Increased risk for thyroid carcinoma related to a positive medical or family history was noted in 15 patients (22.39%). 6 patients had a history of thyroid diseases: Hashimoto thyroiditis (5 patients) and Graves' disease (1 patients). 1 patient had a history of neuroblastoma and had been treated with neck radiotherapy.

Ultrasound results were found in all patients of both groups. The nodule size ranged from 0.3 to 5.3 cm. The mean nodule size was significantly larger in the high-risk group.

Thyroid scintigraphy was performed in 7 patients (10.45%). 6 patients (8.96%) had hypoactive cold nodules and 1 had hyperactive hot nodules.

FNAB was performed in 28 patients (41.79%). The FNAB result was benign in 22 patients (32.84%), non-diagnostic in 3 (4.48%), suspicious in 2 (2.99%), and malignant in 3 (4.48%).

The surgical procedure was performed in 20 patients (29.85%). 5 patients (33.5%) underwent local excision of the suspected nodules, lobectomy was performed in 14 patients (20.9%), and total thyroidectomy was performed in 1 child (1.49%).

Of the 67 patients, 17.91 % ($n = 12$) had thyroid carcinoma in the final pathological analysis.

Conclusion: A thyroid nodule in a child requires an aggressive diagnostic approach due to the increased risk of malignancy.

P2-287**Bone homeostasis in children with subclinical hypothyroidism: Effects of two-years treatment with levothyroxine**

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Background: Thyroid hormone plays a key role in bone mineral homeostasis and significant alterations in its circulating levels have been associated with an impairment in skeletal growth during childhood. To date, the effects of subclinical hypothyroidism (SH) on bones have not been studied and the management of this condition is still debated.

AIM: To evaluate bone mineral density (BMD) in children with mild, persistent SH and the effects of two -years treatment with levothyroxine (L-T4) on skeletal homeostasis.

Methods: Seventeen children (8 males), aged 8.7 ± 1.03 years with mild (TSH levels between 4.2 and 10 mU/l), persistent (≥ 2 years from the diagnosis) and idiopathic SH were enrolled in the study, and compared to 17 age-, sex- and BMI- matched controls. At study entry, both groups underwent clinical examination, laboratory evaluation and dual-energy X-ray densitometry (DXA) scan to evaluate the lumbar spine BMD. Moreover, SH children received 2-year L-T4 treatment and were then reassessed to evaluate possible changes in bone mineral status.

Results: At study entry, mean BMD Z-score was normal in SH subjects and comparable to healthy controls (-0.41 ± 0.42 vs -0.12 ± 0.25 , respectively, p ns). After two years of L-T4 therapy, a mild, but not significant, increase in BMD z-score was observed in SH children, compared to baseline values (0.81 ± 0.56 , p=0.08).

Conclusions: Despite long-term duration, idiopathic SH in children is not associated with impaired BMD, evaluated by lumbar spine DXA. Two-years of L-T4 treatment do not seem to significantly improve BMD in children with SH.

P2-288**The most frequently seen reason of congenital hypothyroidism: Iodine loading**

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Objective: Congenital hypothyroidism; currently, it is one of the most common causes of preventable mental retardation in children. Thyroid dysgenesis, thyroid hormone production and efficacy disorders or temporary hypothyroidism can be seen with the tables. In this study; The aim of this study was to evaluate the etiology and prognosis of congenital hypothyroid patients guided by national screening and neonatal centers. In this way; Our aim is to produce the solution for the causes of transient hypothyroidism

which can be prevented by uncovering the most common causes of congenital hypothyroidism specific to our region and our country.

Materials and Methods: 132 cases of national congenital hypothyroidism screening or treatment were started between 2008-2018 in Gaziantep University Medical Faculty Department of Pediatric Endocrinology; Anamnesis, clinical, laboratory and prognostic features were evaluated. Age, height, weight, gender, thyroid stimulating hormone, free T4, thyroglobulin, iodine concentration in urine, antithyroid antibodies, thyroid ultrasound, scintigraphy, treatment doses and duration of treatment were determined.

Findings: The cases; 68 (51.5%) were female and 64 (48.5%) were male. In the follow-up of these cases; 74 (56%) patients were diagnosed with transient hypothyroidism and 58 patients (44%) with permanent hypothyroidism. In the etiological evaluation of patients with permanent hypothyroidism; Agenesis in 24 (41.4%), hypoplasia in 16 (27.6%), ectopic thyroid in 7 (12%), dishormogenesis in 5 (8.7%), hemiogenesis in 4 (6.9%), and central hypothyroidism in 2 cases (3.4%) detected. In the etiologic evaluation of patients with transient hypothyroidism; Iodine loading in 39 cases (52.7%), iodine deficiency in 23 cases (31.1%) and hypothyroidism due to prematurity were found in 12 cases (16.2%).

Conclusion: This study; In addition to iodine deficiency, iodine loading is an important problem for our country and it is striking that it is first among all causes of congenital hypothyroidism. iodine-containing solutions to the infant (belly care) and to the mother before and after the birth cause iodine overload. For this reason, it is necessary to develop policies throughout the country in order to prevent this situation which creates a serious problem for newborn babies. Iodine levels in urine must be measured in all centers. In this way; In addition to the detection of the problem, there will be a chance to interrupt the treatment to be started earlier.

P2-289

Uncommon Presentations of a Common Condition: Experience from a Teaching Hospital!

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Introduction: Hypothyroidism is one of the commonly diagnosed endocrinopathy in children. The typical manifestations of a hypofunctioning thyroid are lethargy, somnolence, dry skin, cold intolerance, constipation, weight gain and bradycardia along with faltering height. Hypothyroidism presenting with typical manifestations is therefore readily suspected and diagnosed. Occasionally, the patients might present with unusual clinical features which might mimic other conditions thereby delaying the management.

Methodology: This was a retrospective study conducted in the Department of Pediatrics, JNMCH, AMU, Aligarh, India analysing the hospital records between January 2017 till January 2019. The diagnosis of primary hypothyroidism was established by thyroid function tests in all the cases coupled with investigations as required. All the patients diagnosed with hypothyroidism as a work-up protocol for other diagnoses leading to primary diagnosis of hypothyroidism were included.

Observation: A total of 22 children (age 5 years – 16 years; M:F 14:8) were identified as having hypothyroidism associated with other primary manifestations. Three children presented with precocious puberty (Van Wyk- Grumbach syndrome), 2 with ruptured ovarian cyst, 5 with pseudo hypertrophy of calf muscles (Hoffman's syndrome), 2 with psychosis, 1 with Cutis Marmorata, 5 with pericardial effusion and 4 with macrocytic anaemia. Almost all the children had associated short stature though it was not the presenting issue.

The mean time from the occurrence of the symptoms to the diagnosis ranged from 6 months to 6 years (17.9 ± 10.3 months). Mean levels were as follows: TSH 232 ± 57.4 uIU/ml, FT4 0.21 ± 0.09 ng/dl, FT3 1.23 ± 0.63 pg/ml, Anti-TPO antibodies 215 ± 65.35 IU/ml and anti-Tg 454.9 ± 189.3 IU/ml.

The patients were initiated on thyroid hormone replacement and significant improvement in symptoms was observed in all the cases

Conclusion: Awareness about atypical and uncommon manifestations of hypothyroidism is crucial and one needs to consider hypothyroidism whenever confronted with atypical manifestations.

P2-290

A rare combination- Brain Lung Thyroid Syndrome

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A girl, who was born to non-consanguineous Afghan parents, was detected with high TSH on newborn blood spot screening. Her venous blood results had elevated TSH level (31.31mU/L), normal free T4 level (10.2pmol/L) and normal thyroglobulin. Isotope scan showed normal uptake and anatomically normal position of thyroid. L-thyroxin treatment was commenced soon. Since early life she had recurrent respiratory distress and recurrent chest infections needing prolonged oxygen therapy. Her motor development was markedly delayed. Subtle dysmorphisms and central hypotonia was present. Due to the unusual and unexplained combination of these features microarray was done and showed micro-deletion in Chromosome 14 involving NKX2-1 gene associated with Brain-Lung-Thyroid syndrome. The severity of signs and symptoms in our case explains variable expressivity of this genetic condition. Even though mutations in this gene is also associated with movement disorders, this 22 months old girl does not show choreiform movements yet. Her parents are healthy and have normal thyroid profiles. Her rest of blood and urine investigations for developmental delay screening were normal

P2-291**Investigation of Oxidative Effect in Saliva and Gingival Groove Fluids in Children with Hashimoto Thyroiditis**

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The aim of this study was to determine the periodontal health status in patients with Hashimoto thyroiditis (HT) and investigate the gingival groove fluid and saline oxidative stress parameters in order to demonstrate their relationship.

Method: 30 patients between the ages of 11-17 years and 30 healthy volunteers aged between 10-17 years were included in the study. Serum tT4, TSH, anti-TPO, glucose, insulin, ALT, triglyceride, total cholesterol, HDL and LDL cholesterol, ACTH, cortisol and calcium levels were determined in all of the adolescents included in the study. Pocket depth, gingival index, plaque index, presence or absence of hemorrhage during probing was interpreted for periodontal examination.

Results: Gingival groove fluid and saliva total oxidant level levels and salivary oxidative stress index (OSI) were higher in the patient group but no statistically significant difference was found. No statistically significant difference was observed between the groups for periodontal parameters and oxidative stress parameters.

Conclusion: Although the OSI levels in the saliva and gingival cavity were high in the patient group, no statistically significant difference was found. We concluded that periodontal injury process has started and that the process which is continuing in the pathogenesis would end with periodontal disease.

P2-292**Thyroid autoimmunity in children and adolescents with Type 1 Diabetes Mellitus**

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Introduction: Type 1 diabetes mellitus (T1DM) is commonly associated with other organ - specific autoimmune disorders. Autoimmune thyroid disease (AITD) is the most common comorbid autoimmune condition in patients with T1DM. The occurrence of both T1DM and AITD is defined as Autoimmune Polyglandular Syndrome type 3 variant (APS3v). We sought to clarify thyroid autoimmunity in a cohort of Malaysian patients with T1DM.

Methods: A total of 77 patients (42 girls) with T1DM were followed up over time at the Paediatric Endocrine Unit, Hospital Putrajaya, Malaysia from the period of 2001 to 2019. At diagnosis, all the patients were evaluated for beta cell autoimmunity (antibodies to IA-2, ICA and GAD). Thyroid function tests and autoantibodies to thyroid peroxidase (TPO Ab) and thyroglobulin (TG Ab) were evaluated periodically.

Results: The median age of T1DM patients in the cohort was 13[9 – 15.5] years. The median age of diagnosis of T1DM was

7[3 – 10] years with the mean duration of diabetes of 5.9(3.8) years. The prevalence of AITD in the cohort of T1DM patients was 6.5%. One patient was diagnosed with Graves disease prior to the diagnosis of T1DM. The rate at which at least one of the thyroid autoantibodies tested positive (TPO Ab or TG Ab) was 35.3% T1DM/AIT(+). Further analysis revealed, 26.4% had only positive TPO Ab, 2.9% had only positive TG Ab and 8.9% were positive for both TPO Ab and TG Ab. In binary logistic regression analysis, antibodies to GAD was a significant risk factor for the development of thyroid autoantibodies . Additionally, female sex, an older age onset of T1DM, and a higher prevalence of antibodies to GAD were significantly observed in the T1DM/AIT(+) group.

Conclusion: This study demonstrates several differences in the clinical characteristics of T1DM patients with or without thyroid autoimmunity. This finding may indicate a distinct genetic background of these subset of patients and may shed light in the understanding of the pathogenesis of these conditions.

P2-293**Analysis of diabetes-associated autoantibodies in children and adolescents with autoimmune thyroid diseases**

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Background: Zinc transporter 8 autoantibodies (ZnT8Abs) together with glutamic acid decarboxylase autoantibodies (GAD-Abs), insulinoma antigen 2 autoantibodies (IA-2Abs) and insulin autoantibodies (IAbs) are markers of type 1 diabetes mellitus (T1DM). We studied the prevalence of ZnT8Ab in children with autoimmune thyroid diseases (AITDs) to assess the association of AITDs and T1DM at the serological level.

Methods: The study groups consisted of 44 children with Graves' disease (GD), 65 children with Hashimoto's thyroiditis (HT), 199 children with T1DM with or without AITDs and 58 control children. ZnT8Ab, GADAb, IA-2Ab, IA, 21-hydroxylase autoantibodies (21-OHAbs) and acetylcholine receptor autoantibodies (AChRAbs) were measured.

Results: ZnT8Abs were found in 4/44 (9.1%) patients with GD, and 4/44 (9.1%) patients with GD were positive for GADAb. Of the 65 HT patients, six (9.2%) were positive for ZnT8Ab, while four (6.2%) were positive for GADAb. In the T1DM group, 128/199 (64%) of the patients were positive for ZnT8Ab, 133/199 (67%) for GADAb and 109/199 (55%) for IA-2Ab. One GD patient and one HT patient were positive for all the four diabetes-associated autoantibodies. Two HT patients were positive for three diabetes autoantibodies. Two GD (4.5%) and five HT (7.7%) patients were positive for 21-OHAb only. None of the patients had AChRAb. In the control group, 2/58 (3.4%) were positive for GADAb and 2/58 (3.4%) were positive for ZnT8Ab.

Conclusions: Diabetes-associated autoantibodies including ZnT8Ab were found in children and adolescents with GD and HT.

P2-294

A new case of thyroid hormone resistance α caused by a mutation of THRA/TRα1

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The action of Thyroid hormone (T3) is mediated by the binding to nuclear receptors (TR α 1, TR β 1/2), which are ligand dependent transcription factors, encoded by the THRA and THRB genes. THRA germline mutations cause a rare genetic disease called resistance to thyroid hormone α (RTH α) first reported in 2012. Only 20 missense and frameshift mutations have been reported to date. From this small group of patients, and analysis of animal models, it emerges that the disease severity correlates with the inability of the receptor to release transcription corepressors in the presence of T3. This can result either from a decrease in the affinity of TR α 1 for T3, or from an alteration of its C-terminal helix, which normally recruits transcription coactivators upon T3 binding, releasing corepressors.

We report here the first discovery of a patient with RTH α in China. The patient is the first and only child of healthy unrelated parents. This boy was born at full-term by vaginal delivery. His developmental milestones were delayed. He walked at eighteen month and knew only two words at 2 years (mama and baba). Poor coordination and clumsiness were noted. He had chronic constipation.

On examination at 2 years, his height was 80cm. He was disproportionately short, with short arm span (78cm). The heart rate was low. His skin was thick without skin tags. The face and nasal bridge were broad, but there was no macroglossia.

Results of the screening tests for metabolic defects, including blood and urine amino acids analysis and urinary organic acid analysis were normal. Routine karyotyping(G-bands) showed 46,XY.

The ultrasonic thyroid pelvic were normal. Head and pituitary MRI appeared normal. Radiographic studies showed a normal morphology of the vertebral column, DNA sequencing, using Target Region Sequencing and Sanger sequencing revealed that the patient was heterozygous for a THRA mutation (c.1183G>T, p.E395X) absent in parents.

The initial dose of L-T4 was ordered to 25 g/day. About half a year later, his motor coordination remained poor, and clumsiness was visible.

The E395X mutation eliminates the C-terminal helix of TR α 1 and is thus expected to display consequences similar to the C392X, F397fs406X, E403X mutations, which exert a strong dominant-negative influence in heterozygous cells. For this type of mutation, L-T4 treatment provides little benefit, and the manifestations of RTH α are severe. This report also outlines the variability in RTH α manifestations, the large head circumference, which was reported for several other patients, was absent.

P2-295

The incidence of congenital hypothyroidism during the neonatal screening program in the Republic of Karakalpakstan, Uzbekistan

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Background: In the world, the incidence of congenital hypothyroidism varies in wide ranges. In the neonatal screening based on thyroid-stimulating hormone (TSH), the optimal diagnostic level of TSH is essential to ensure that the true cases of congenital hypothyroidism are not missed.

The goal was to compare the incidence rate of congenital hypothyroidism during the course of changes in the screening protocol for the periods of 2003-2007 and 2008-2017.

Materials and Methods: During 2003-2007, the diagnostic level of TSH from capillary blood on the 4th-5th day was > 20 microU/ml of whole blood, then a repeated serum retest was recommended on the day 15. Congenital hypothyroidism was diagnosed at TSH level > 10 microu/ml, and it was recommended to start an immediate treatment with thyroxine.

During 2008-2017, the protocol was changed: the recommended diagnostic level of TSH from capillary blood on day 4-5 was > 10 microU/ml of whole blood, after which the retest from blood serum on day 15 was prescribed. If the serum TSH level was > 5 microU/ml, then it was necessary to immediately begin treatment with thyroxine.

Results: A total of 313,970 newborns were examined in the Republic of Karakalpakstan. During 2003-2007, the incidence of congenital hypothyroidism in the region was 1:3185, whilst in Uzbekistan it was 1:2350. After changing the screening protocol, in the years of 2008-2017, the incidence of congenital hypothyroidism in Karakalpakstan leveled at 1:2280, and in the country overall at 1:3215. For the entire period, 129 children with congenital hypothyroidism were identified in Karakalpakstan. In their third year of life, 95 were left registered, 25 children were taken off the registry due to transient hypothyroidism, 3 left, and 3 died.

Conclusions: It was revealed that the incidence of congenital hypothyroidism in Karakalpakstan is higher than in Uzbekistan as a whole. Changing the screening protocol improved the diagnosis of the disease.

P2-296

Progressive thyroid dysfunction in infants with Down Syndrome; Trisomy 21 (DS): Effect on Linear Growth

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Hypothyroidism is the most frequent thyroid abnormality in DS. It can be either congenital, with or acquired at any age after birth. It can be clinical or subclinical disorder. More evidence is required regarding the progressive development of thyroid dysfunction with age.

Aim and Methods: We measured thyroid function (Free T4 and TSH) and Anti TPO level in 37 infants with DS at birth, during their first year and after ~ 2.5 years of age. Their linear growth (Length (L), weight (Wt), LSDS, BMI and BMISDS were measured and analyzed in relation to their thyroid function. Overt hypothyroidism was diagnosed with (low Free thyroxine [FT4] (<9 pmol/L) and increased thyroid-stimulating hormone [TSH] levels >10 µIU/ml); and subclinical hypothyroidism was diagnosed with (normal FT4, and TSH between > 15 µIU/ml at birth and > 10 µIU/ml during infancy and childhood)

Results:

Table 1. Progressive thyroid dysfunction in infants with DS during infancy and early childhood.

Age	Hypothyroid	Subclinical Hypothyroid	Normal
Birth	1/37 (2.7%)	1/37 (2.7%)	35/ 37(94.6%)
0.45 +/- 0.36 y	3/37 (8%)	9/37 (24.3%)	25/37 (67.5%)
2.7 +/- 1.5 y	4/37 (10.8%)	11/37 (29.7%)	22/37 (59.5%)

Table 2. Linear growth in DS with thyroid dysfunction versus DS with normal thyroid function

	DS with Thyroid Dysfunction	DS with Normal Thyroid function
Number	12/37	25/37
L SDS1	-1.5 +/- 1.4	-1.57 +/- 1.4
BMI1	14.4 +/- 2.5	14 +/- 2.3
BMISDS1	-1.1 +/- 1.4	-1.45 +/- 1.5
L SDS2	-2 +/- 0.6	-1.7 +/- 0.8
BMI2	16.4 +/- 1.6	16 +/- 1.9
BMISDS2	0.4 +/- 1.3*	0.2 +/- 1.35*

1: at 0.45 years, 2: at 2.7 years, *p< 0.05 same group after follow up, # p< 0.05 between groups

Discussion: The incidence of thyroid dysfunction in our infants with DS at birth was 1:37 (2.7%) was higher than the reported incidence in other studies and compared with an incidence of congenital hypothyroidism in our country (1: 2150) among newborns without DS. There was a progressive increase in thyroid dysfunction in our DS children especially during the first year of their life.

At an average of 2.7 years ~ 40% of them had thyroid dysfunction. At this age 3/37 had positive Anti-TPO; two of them had thyroid dysfunction. Females had more thyroid dysfunction versus males (11/15 versus 4/15 respectively)

Conclusion: Thyroid dysfunction is common in infants with DS especially developing during the first year of life. Early management of thyroid dysfunction is associated with normal linear growth compared to those with normal thyroid function.

P2-297

Evaluation of elevated serum a Thyroid-Stimulating Hormone (TSH) in children and adolescents: A single-center study in Uruguay

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Introduction: primary hypothyroidism is the most frequent thyroid disease in children, and elevation of serum TSH is a common presenting complaint (pc) in the pediatric endocrinology outpatient clinic. Subclinical hypothyroidism (sHT) predominates in relation to overt hypothyroidism (cHT). The benefit of Levothyroxine is controversial specially when serum TSH levels are less than 10 uUI/ml.

Objectives: to evaluate the prevalence of children with elevated serum TSH referred to our center in a period of 6 months (January to June 2016). Analyze patient characteristics, biochemical diagnosis and treatment with Levothyroxine.

Methods: a retrospective, cross-sectional study was performed based on review of the charts of children between 2 and 15 years with elevated serum TSH in the pediatric endocrinology outpatient clinic at the Pereira Rossel Hospital, Montevideo Uruguay. Final population was 72 children. Data collected was: age, gender, anthropometry: height and body mass index (BMI), goiter, neurodevelopment, main reason of request serum TSH. Biochemical values of: TSH, free thyroxine (fT4), anti-thyroid autoantibodies (anti-Tab), second thyroid profile and treatment with Levothyroxine.

Results: fifty percent of the pc were because of elevated serum TSH and the main reason of request was the obesity. No significant difference was between sex, and age of presentation was 7 years. Seventy-five children had normal neurodevelopment. Almost half of the patient had overweight or obesity (15% and 33% respectively) and no one of this associated impaired growth. Biochemical diagnosis was made with the fist thyroid profile: 11% cHT and 88.9% sHT. The second profile was made in 47% of the sHT and the serum TSH level normalized in 13.6%. There was a statistically significant decrease between the first and second TSH value (p = 0.01). The prevalence of sHT was 22.3% due to a correct diagnosis. All of the cHT and sHT with TSH ³ 10 uUI/ml received treatment with Levotiroxine. Fifty eight percent of the sHT with serum TSH levels < 10 uUI/ml were treated but only 48% of them had a confirmatory profile.

Conclusions: half of the children referred to our center had elevated serum TSH. Obesity was the main cause of solicitude serum TSH and sHT was the most prevalent diagnosis. In most of

the cases the diagnosis was not made correctly leading to an over diagnosis and over treatment.

Key words: subclinical hypothyroidism, obesity, children, Levothyroxine.

P2-298

Neonatal hyperthyroidism: our centre's experience

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Objective: Neonatal hyperthyroidism is a severe but generally transient condition with a 2% prevalence in offspring of mothers affected by Graves' disease. It is caused by the transplacental passage of maternal anti-thyrotropin receptor stimulant antibodies (TRABs). Here we report the cases diagnosed at our centre between 2015-2019 in order to re-evaluate the diagnostic and therapeutic approach to this challenging neonatal thyroid alteration.

Methods: The study was conducted on a cohort of twenty newborns diagnosed with neonatal hyperthyroidism. All had mothers who were or had been affected by Graves disease. We collected the records of the maternal disease and treatment during pregnancy along with data regarding the birth, diagnosis, and treatment of the newborn.

Results: Three mothers (15%) underwent total thyroidectomy and were in substitutive treatment with L-Thyroxine during pregnancy. None of these three cases had available maternal TRABs values. In 3rd-4th days of life these three newborns developed hormonal and clinical signs (hypertonus/exophthalmus/tachycardia) of hyperthyroidism with an important elevation of TRAB values (>17 to 72 times the upper reference limit). Thus Methimazole (MMZ) was started and associated, in two cases, with a beta-blocker therapy.

An anti-thyroid drug (MMZ or Propiltiouracile) was prescribed before or during the gestation in seventeen mothers (85%). Maternal TRAB values were only reported in eight pregnancies, all resulting positive. Between the 3rd and 21st day of life the diagnosis of neonatal hyperthyroidism was confirmed by thyroid function tests; neonatal TRABs values resulted positive in all the newborns. MMZ treatment was started in nine infants (53%) while the others had a spontaneous remission.

Conclusions: The determination of maternal TRABs levels is essential in order to identify the newborns at risk of developing neonatal hyperthyroidism, a rare and potentially life-threatening condition. Nevertheless, this dosage is often disregarded, especially in mothers that previously underwent a total thyroidectomy. We observed that elevated neonatal TRABs values seem to be associated with more severe clinical and hormonal features requiring treatment. Less severe and belated forms are generally present in the offspring of mothers taking anti-thyroid drugs, with lower neonatal TRABs levels and not always requiring anti-thyroid therapy.

P2-299

Epidemiological aspects of pediatric thyroid disorders in Western Ukraine

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Introduction: Thyroid disorders (such as endemic and nodular goiter, thyroiditis, congenital and acquired hypothyroidism) are one of the most common endocrine problems in children and adolescents in Ternopil Region (Ukraine) during the last decades. The main causes of goiter in children may include autoimmune diseases and iodine deficiency.

Purpose: The aim of current study is to assess goiter according to etiology in the pediatric population of Ternopil region and propose a prevention strategy.

Methods: A retrospective analyses of statistic medical forms (official database) in Ternopil region has been conducted.

Results and Discussion: The study shows that in spite of reduction of children's population (0-17 years old) from 215 thousands in 2008 to 199 thousands in 2018 morbidity and distribution of thyroid pathology permanently increase (Table).

Table. Morbidity and distribution per 1000 children in population

Disease	2008 year		2018 year	
	Morbidity	Distribution	Morbidity	Distribution
Goiter 1 grade	17.77	43.22	18.56	43.56
Goiter 2 grade	1.02	4.28	0.94	5.06
Autoimmune thyroiditis	0.13	0.25	0.14	0.58
Nodular goiter	0.09	0.28	0.12	0.29
Hypothyroidism	0.03	0.21	0.18	0.65

Taking into account that in our endemic area population commonly use either non-iodized salt or iodized salt, we can assume direct effect of such tradition to the tendency in morbidity and distribution of thyroid pathology.

According to governmental database in Ternopil region, the amount of affected children from 0 to 18 years is around 4.9 to 5.7 % of whole population. It is well known fact, that the main cause of euthyroid goiter 1 and 2 grade is iodine deficiency. By WHO guideline (2007, Geneva) it is recommended that a total goiter rate (number with goiters of grades 1 and 2 divided by total examined) of 5% or more in schoolchildren 6 to 12 years of age be used to signal the presence of a public health problem.

Conclusions: Summing up what has been presented, iodine deficiency could not be clearly confirmed in our region. So, current study should to be continued in target group of children with urine iodine determination to implement a regional program to eliminate probable iodine deficiency disorders.

P2-300**The encephalopathy as complication of Hashimoto thyroiditis in children: a wide variety of clinical manifestations**

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Hashimoto encephalopathy is an autoimmune encephalopathy predominantly diagnosed in the adult population. In the pediatric population, the mean age is determined to be 14 years, with the majority of adolescent females. The diagnosis of Hashimoto encephalopathy is clinical and based on the highly variable neuropsychiatric conditions, often affecting more than one area of the central nervous system, the detection of antiperoxidase or antithyroglobulin antibodies in serum, and on the elimination of other potential etiologies. The pathophysiology of Hashimoto encephalopathy is still unclear; autoimmune and vasculitic mechanisms can play an active role. A clinical response to corticosteroid therapy is supportive of the diagnosis. The occurrence of Hashimoto encephalopathy is unrelated to the patient's thyroid function status. Neuroimaging studies, EEG, and cerebrospinal fluid analysis can be supportive, although they are not diagnostic. MRI studies in children have mostly shown prolonged T2-weighted signals of the subcortical white matter, suggesting inflammation or demyelination.

The current standard treatment is the use of corticosteroids in addition to the treatment of any concurrent dysthyroidism. Other options are immunoglobulins and plasmapheresis.

We describe the case of a 17-year-old girl who admitted due to headache followed by hearing loss and disorientation in depression status and anorexia nervosa with significant weight loss. She had a 8-year history of celiac disease. She had normal general and neurological examination, height 160 cm (25-50 pc), weight 37 kg (<3 pc), and body mass index 14.5 kg/m² (< 3 pc). She had normal transglutaminase IgA antibody, significantly elevated thyroperoxidase (TPO) antibody titers 5.674U/mL in euthyroid function, consistent with the diagnosis of Hashimoto's thyroiditis. The analysis of cerebrospinal fluid showed high protein level and TPO antibodies. Cerebral MRI showed T2 hyperintensity in the periventricular white matter. Electroencephalography was normal. Steroid therapy was initiated with methylprednisolone intravenously for 3 days, followed by prednisone orally.

Encephalopathy as a complication of Hashimoto thyroiditis was first described by Brain and Coworkers in 1966 in the adult patient. In recent years have been increasingly recognized in both adult and pediatric patients. Particularly, the association between neuropsychiatric symptoms and Hashimoto thyroiditis should lead to early suspicion of this disorder. Prodromal headache and sensori-neural hearing loss have been reported in the autoimmune encephalitis. Therefore, this case report aims to raise awareness about the extreme variability of the clinical spectrum of the Hashimoto encephalopathy especially in the presence of a known autoimmune disease and the importance of multidisciplinary approach for a early recognition.

P2-301**Acute-onset peripheral polyneuropathy in a 12-year-old girl due to Hashimoto thyroiditis: traps in the diagnosis**

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Introduction: Thyroid dysfunction may cause a wide range of neurological disorders in children. Hypothyroidism is associated with peripheral nerve demyelination. However, minimal data are available in pediatric population.

Purpose: To describe a case of newly diagnosed Hashimoto thyroiditis (HT) suffering acute-onset rapidly progressive peripheral polyneuropathy.

Case Report: A 12-year-old girl presented for the first time to our Department because of a 2-week history of left upper limb weakness and paresthesia. She was newly diagnosed with mild hypothyroidism due to HT and started on levothyroxine (LT4). On physical examination, she had diminished touch sensation on left upper limb and bilateral absence of knee reflexes. Electrophysiological study was indicative of acute sensory polyneuropathy and cerebrospinal fluid (CSF) examination revealed slightly elevated albumin with normal cell count. Based on these findings, the patient received intravenous immunoglobulin treatment with the suspicion of Guillain-Barré syndrome. The following days clinical deterioration was recorded; she had wide based standing, her gait was slightly ataxic and she developed acute onset moderately severe, continuous, burning pain affecting her left foot. Meanwhile, thyroid function evaluation questioned the need for LT4 substitution therapy since thyroid stimulating hormone levels were suppressed and free thyroxine concentration was elevated; HT was confirmed by high titers of antithyroid antibodies. Further detailed history and physical examination revealed signs and symptoms of hyperthyroidism (weight loss, tremor, anxiety, sleeplessness, palpitations, diarrhea). Based on negative thyroid stimulating immunoglobulin a diagnosis of iatrogenic hyperthyroidism was made. LT4 was discontinued and beta-blocker was prescribed because of severe tachycardia and hypertension leading to gradual clinical and biochemical improvement. Despite the normalisation of thyroid hormones, deterioration of weight loss and neuropathic pain alongside with secondary amenorrhea necessitated further evaluation of sensory polyneuropathy including anorexia nervosa. Potential causes of neuropathy (vitamin deficiency, metabolic, toxic, infectious, inflammatory, autoimmune, paraneoplastic, inherited) were excluded. On 6-month follow-up, the patient is euthyroid, while signs and symptoms of hyperthyroidism have resolved; she gained the lost weight and her menstruation normalised; however, glove and stocking distribution neuropathy has improved but persists. Based on this clinical course, HT can be considered the cause of neuropathy explaining also the slightly elevated CSF albumin levels.

Conclusion: This case experiencing the wide spectrum of thyroid dysfunction, from hypothyroidism to hyperthyroidism and finally to euthyroidism underlies the necessity of thyroid function evaluation in children with acute polyneuropathy. Symptoms of neuropathy may precede the diagnosis of hypothyroidism and persist despite normalisation of thyroid hormone levels.

to his normal habitus, and there was no clinical feature of Cushing syndrome. The resolution of Cushing syndrome after the Wilms' tumor was treated showed that this was likely a case of paraneoplastic Cushing syndrome. The challenge lies in the diagnosis and the management of steroid therapy post-operatively. We also highlighted the patient's peculiar cortisol secretory pattern and his response to both dexamethasone suppression tests.

Poster Category 3

Adrenals and HPA Axis

P3-1

A case of Cushing syndrome in a Wilms' tumour

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Paraneoplastic Cushing syndrome is extremely rare. To date, there are few reported cases related to Wilms' tumor. We describe a patient who presented with Cushing syndrome and was subsequently found to have Wilms' tumor. Our patient is a 9 year-old boy, who presented with hyperphagia and excessive weight gain for 3 months. His abdomen was also progressively bigger. There was no ingestion of steroids or traditional medication. Subsequently he sought medical advice because of persistent cough and was found to be hypertensive with features of Cushing syndrome. On physical examination, his height was 123cm (50-75thcentile) and his weight was 32.3kg (90-97thcentile). He had features of Cushing syndrome with moon-like facies and buffalo hump. There was a firm bablettable mass in the left upper quadrant region. A Computed Tomography of the abdomen revealed a 9.2 x 12.7 cm mass arising from the upper pole of the left kidney likely to be Wilms' tumor. The adrenal glands could be visualized and looked normal. We proceeded to perform a low dose dexamethasone suppression test followed by high dose dexamethasone suppression test. The low dose dexamethasone suppression test confirmed the diagnosis of Cushing syndrome (not adequately suppressed). His cortisol level was suppressed during high dose dexamethasone test which suggest pituitary Cushing disease. However, his Magnetic Resonance Imaging of the pituitary gland was normal. His ACTH level was 9.2 pmol/L. The patient underwent a left radical nephrectomy and partial adrenalectomy. He was covered with stress dose of hydrocortisone peri-operatively. Biopsy showed Stage I Wilms' tumor (Blastemal predominant). Immunohistochemistry for ACTH was negative in the tumor cells. We were not able to perform immunohistochemical studies for CRH. His hydrocortisone was eventually weaned off. By a year after the operation, he was back

P3-2

A rare cause of primer adrenal insufficiency: *NROB1 (DAX1)* mutation

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Introduction: Congenital adrenal hypoplasia, a rare cause of childhood primer adrenal insufficiency, is caused by defects in transcription factors involved in the development of adrenal gland. One of them is the *NROB1 (DAX1)* gene, localized in Xp21.2. *DAX1* mutations have been identified that cause X-linked adrenal hypoplasia congenita. Infants affected with X-linked adrenal hypoplasia congenita may present with salt-wasting, micropenis or cryptorchidism. Moreover, delayed puberty and infertility due to hypogonadotropic hypogonadism caused by *NROB1 (DAX)* mutations have also been reported. We would like to present a two-months-old male diagnosed with primer adrenal insufficiency due to a nonsense mutation in *NROB1 (DAX1)*.

Case: A two-months-old male was brought to the emergency department because of abnormal eye movements and suspicious of seizure. He was born to nonconsanguineous parents at term with a birth weight of 3400 gr. Five brother of the mother had died during neonatal period due to unidentified etiology. Physical examination was unremarkable except for mild dehydration. Genital examination revealed normal male external genitalia. His weight was 4000 gr (3-10th centile), height was 58 cm (50-75th centile), and blood pressure was 85/60 mmHg. Laboratory examination revealed hyponatremia (115 mmol/L), hyperkalemia (7.5 mmol/L), hyperreninemia, high ACTH (1094 pg/mL) and relatively low cortisol (8.1 µg/dl) levels. The diagnosis of primer adrenal insufficiency was established and hydrocortisone and fludrocortisone were started. Moreover, serum levels of 17-hydroxyprogesterone, DHEA-S, 11-deoxycorticosterone and 1,4-androstenedione were in normal range. The diagnosis of congenital adrenal hyperplasia (CAH) was excluded. Molecular genetic analysis of *NROB1 (DAX1)* revealed a hemizygous non-sense mutation [c.1282G>T (p.Glu428Ter)].

Results: Genetic defects in *NROB1 (DAX1)* have been reported in two thirds of male cases with undiagnosed primary adrenal insufficiency. Therefore, all male patients with non-CAH primary adrenal insufficiency should be screened for *NROB1 (DAX1)* defect.

A 46, XX patient with 21-OHD diagnosed during the etiologic workup of male infertility

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Introduction: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders of the steroid biosynthesis. 21-hydroxylase deficiency (21-OHD) represents 90–95% of CAH patients and causes adrenal insufficiency and virilization. Although most patients are diagnosed in childhood, the diagnosis of some classical CAH cases are extremely delayed up to sixth and seventh decades of life. Herein, we report a 46, XX patient with 21-OHD diagnosed during the etiologic workup of male infertility.

Case Report: A 32-years-old male patient was referred due to infertility. His parents were second degree cousins, he or his family had no history of any chronic disease. He a deceased 4 years old brother of an unknown cause. The physical examination of the patient revealed genital hyperpigmentation, bilateral cryptorchidism, the phallus was approximately 3 cm and had no hypospadias. Ultrasonography revealed a hypoplastic uterus (61x13 mm) but no ovarian tissue. The biochemical data suggested CAH due to 21-OHD (Table 1). His karyotype was 46, XX and SRY was negative. Genetic testing demonstrated homozygous CYP21A2 A/C-656>G mutation. Steroid replacement and surgical management were planned but the patient refused treatment.

Conclusions: Although classical 21-OHD may cause a life threatening salt-wasting crises in early infancy and childhood, some cases may have atypical delayed presentations. This may potentially be due to compensatory effect of adrenal steroid hormone precursors that accumulate and transactivate glucocorticoid receptor, and mask cortisol deficiency. Detailed genital examination should be a part of diagnostic approach in order to recognise adrenal causes of infertility.

Table 1. Biochemical characteristics of the patient

FSH (mIU/ml)	0.26 (1.9-18.9)
LH (mIU/ml)	<0.1 (1.7-9.6)
E ₂ (pg/ml)	72.7
Total Testosteron (ng/dl)	1075
ACTH (pg/ml)	469 (<46)
Cortisol (ng/ml)	35.68 (50-250)
Na (mmol/L)	124 (135-145)
K (mmol/L)	3.8 (3.5-5.2)
17-OH Progesteron (ng/ml)	186.89 (0.42-1.96)
DHEA (ng/ml)	6.87 (0-10)
DHEA-S (ng/ml)	1084.63 (650-3340)
Androstenodione (ng/ml)	46.05 (0.4-1.5)
Testosterone (ng/ml)	4.81 (2.4-9.5)
Dihydrotestosterone (ng/ml)	0.21 (0.16-0.79)
Corticosterone (ng/ml)	0.96 (0.53-15.6)
11-deoxycorticosterone (ng/ml)	<0.053 (0-0.15)
11-Deoxycortisol (ng/ml)	0.64 (0.1-0.79)
Aldosteron (ng/ml)	0.04 (0-0.21)
Progesterone (ng/ml)	1.57 (0.2-1.4)
Pregnenolone (ng/ml)	0.78 (0.3-2.08)
17-OH Pregnenolone (ng/ml)	1.88 (0-1.28)
Estradiol (ng/ml)	0.2 (0.02-0.06)

A female infant with severe salt-wasting due to aldosterone synthase deficiency, initially mimicking adrenal insufficiency

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Background: Correct diagnosis of the etiology of adrenal deficiencies is essential for appropriate treatment.

Case Report: At the 12th day of life, the girl had suffered an episode of severe salt wasting with marked hyponatremia (109 mmol/l) and hyperkalemia (6.9 mmol/l). Under the assumption of adrenal insufficiency therapy with hydrocortisone and fludrocortisone as well as salt had been started. Unfortunately, due to the emergency character of this situation, there had been no prior evaluation of ACTH and cortisol.

At the age of one month, the patient was referred to us by an external clinic for further diagnostic work up. We performed an ACTH stimulation test in the morning before medication to further evaluate adrenal function. She showed an insufficient

response with a stimulated cortisol of 3.6 µg/dl, so primary adrenal insufficiency was suspected. Chromosome analysis showed a normal 46, XX karyotype.

Levels of ACTH and cortisol were tested repeatedly in the morning before medication and showed normal. Plasma renin activity was elevated, so we considered isolated deficiency of mineralocorticoid biosynthesis. In the molecular genetic analysis two mutations in the *CYP11B2* gene (aldosterone synthase) could be detected. The two mutations c.892_893delinsTG; p.Glu298X and c.1235G>C; p.Arg421Pro have not been described before. The parents are both heterozygous carriers for the mutations.

A second ACTH stimulation test was performed. This test demonstrated a normal rise of cortisol level to 23.8 µg/dl. Thus, sufficiency of ACTH-cortisol axis could be proven. Hydrocortisone was gradually reduced and discontinued. Urinary steroid metabolome analysis by GC-MS revealed the typical biochemical constellation of aldosterone synthase deficiency type 1. To date, fludrocortisone is given and our patient is developing well.

Conclusion: The need for sampling of plasma and urine for the determination of the decisive endocrine parameters is strongly recommended before starting emergency hydrocortisone therapy.

We detected two novel mutations in the *CYP11B2* gene (p.Glu298X and p.Arg421Pro) leading to aldosterone synthase deficiency.

The baby was discharged at 5 weeks of age in good general condition and is followed up regularly in the pediatric endocrinology department.

In CAH deficient fetal cortisol production leads to overproduction of ACTH, stimulating the disordered fetal adrenal to produce excess androgens, virilizing female fetuses at 7-12 weeks gestation; however development of the ovaries, uterus and fallopian tubes remains normal.

Supraphysiological doses of exogenous steroids are required to suppress androgen excess and it was shown that prenatal dexamethasone treatment of fetuses at risk of congenital adrenal hyperplasia can prevent virilization of a female fetus. This treatment has since been offered at the dose of 20 mcg/kg maternal body weight per day, to avoid the need for feminizing genital reconstructive surgery and the risk of complications, and remains controversial. However, this treatment has shown a success rates of 85%. The long-term effects of steroids in early pregnancy remain unclear, with potential detrimental effects on fetal programming, brain function and congenital anomalies.

In this case, although the baby has a severe form of salt-wasting CAH, at birth she has minimal virilization (Prader stages I-II). We hypothesize that maternal therapy with prednisone at low dose since the beginning of the gestation, partially prevented virilization of the child genitalia.

P3-5

Can early prenatal prednisone treatment reduce virilization of CAH female newborn?

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A female second born of unrelated parents, at fourth pregnancy, born by vaginal delivery at 39 weeks of gestational age, weight 3145 g (-0.45 SDS), length 50 cm (0.12 SDS), head circumference 33 cm (-0.82 SDS), presented with DSD. The mother affected by hypothyroidism and autoimmune hepatitis, during the whole pregnancy was treated with levothyroxine and prednisone at the dose of 5 mg/day. At birth mild ambiguous genitalia (Prader stages I-II) were noticed and the baby was admitted to neonatology department for clinical assessment.

Laboratory tests showed high levels of 17hydroxyprogesterone (510 ng/ml), ACTH (329 pg/ml) and testosterone (9 ng/ml). Ultrasound of the abdomen showed normal uterus and ovaries. After genetic counseling, karyotype, analysis for SRY and CYP21 genes were performed. The exams confirmed the diagnosis of congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency [655 I2 Splice (C>G) intron2; R356 W (exone 8)] in a newborn with a female karyotype of 46, XX. Cystourethrography has not been performed yet.

Therapy with hydrocortisone was started with subsequent reduction of 17hydroxyprogesterone, ACTH and testosterone levels. At 1 months of age she presented a salt-wasting crisis, so replacement therapy with fludrocortisone and sodium solution was added.

P3-6

Clinical characteristics and etiological diagnosis of premature pubarche among 55 children

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Objective: To understand the clinical characteristics, etiological distribution and related metabolic problems of children with premature pubarche.

Methods: The clinical data of 55 cases of premature pubarche were summarized. All the children were tested by ACTH stimulation test and GnRH stimulation test, of which 17 cases were detected by CYP21A2 gene, and 16 cases of Premature Adrenarche (PA) and 14 cases of Isolated Premature Pubarche (IPP) were analyzed by metabolic profile.

Results: 9 of 55 children with premature pubarche were diagnosed as Nonclassical Congenital Adrenal Hyperplasia (NCCAH). There was no significant difference in the diagnostic rate of NCCAH between ACTH stimulation test and CYP21A2 gene detection ($P=0.596$). The etiological analysis showed that 19 cases were diagnosed as Central Precocious Puberty (CPP), 30 cases were diagnosed as PA (16 cases were simple PA), and 14 cases were diagnosed as IPP. 16 cases simple PA, 14 cases IPP and 20 cases of control normal children were analyzed by metabolic profiles. The results showed that the sex hormone binding protein (SHBP) in the PA group was lower than that of the control group ($P=0.007$), while the free androgen index (FAI), fasting blood glucose (FBG) and insulin resistance index (HOMA-IR) were all increased ($P=0.002$,

0.040 and 0.038, respectively). There was significant difference in BMISDS between the IPP group and the control group ($P=0.007$), but the difference of SHBP, FAI, FBG and HOMA-IR were not significant (all P value was greater than 0.05).

Conclusions: The etiology of premature pubarche are Premature Adrenarche, followed by Central Precocious Puberty, Isolated Premature Pubarche and Nonclassical congenital adrenal hyperplasia. The ACTH stimulation test is useful for the diagnosis of NCCAH, but the sensitivity is not 100%. The children with PA may be a forerunner of metabolic syndrome, long-term follow-up is important.

Keywords: Premature Pubarche, ACTH stimulation test, Non-classical congenital adrenal hyperplasia, Premature Adrenarche

P3-7

Rare case of cortisol producing tumour in 14 years old girl

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Background: Adrenocortical Carcinoma (ACC) represents 0.16% of all pediatric neoplasm in children, 0-14.9 years, diagnosed between 1984-2010 according to Swedish Childhood Cancer Registry. ACC is most frequent in girls below 4 years of age.

Case: A physically active 14 years old girl was referred due to growth velocity 0 cm over the last year. Her history revealed substantial weight gain (photos), pubertal arrest premenarche and increased body hair.

Clinical signs: Cushing Syndrome with increased abdominal fat, hirsutism, acanthosis nigricans and acne in face and shoulders. Height 160.4 cm, weight 62 kg, BMI 24.1 and pubertal stage Tanner B3, PH5.

Investigation: Serum-lab: Cortisol 521 nmol/L, Testosterone 3.7 nmol/L (<1.8), DHEAS 15.4 µmol/L (1.8-10.0), 17-OHP 2.3 nmol/L (<5-18).

At midnight ACTH <0.3 pmol/L (1.5-14), Cortisol 542 nmol/L (<50), without diurnal variation.

Dexamethasone suppression test 1 mg and 9hrs later: morning S-Cortisol 632 nmol/L and Saliva Cortisol 9.85 nmol/L (<3).

24hrs U-Cortisol 1406 nmol/L (<170), U-Steroid profile showed high androgen and cortisol production. Genetic syndromes as Beckwith-Wiedemann, Li-Fraumeni, MEN1 and Carney Complex that predispose for cancer development were excluded. MRT of the adrenals shows a non-fatty 5x5x4 cm tumour in the right adrenal.

Treatment: Surgery: The tumour was resected together with the right kidney and a part of the liver. Pathologists found an adrenocortical carcinoma invading the capsule of the liver. No sign of metastasis or rest-tumour was shown by Metomidate-PET.

Chemotherapy: 8 blocks of multiple drug chemotherapy for 6 months, combined with 18 months of mitotane treatment for inhibiting steroid synthesis and for cytotoxic effect on the adrenal cortex. Hydrocortisone replacement started directly postoperative and continues. The therapeutic window for mitotane was

difficult to maintain due to side effects, especially nausea. Mitotane is stored in the fat tissue and released during weight loss, resulting in mitotane remaining in suppressive serum concentration for 20 months after end of treatment.

Observation time is presently 4.5 years with no sign of relapse.

Summary: A case of non-syndromic adrenocortical carcinoma in a 14 years old girl presenting with growth failure and Cushing syndrome. Mitotane treatment was challenging with the substance still detectable in suppressive serum concentration during 20 months after end of treatment. Ongoing hydrocortisone replacement will probably be lifelong.

P3-8

Typical phenotype of isolated aldosterone synthetase (AS) deficiency in two infants with heterozygous AS gene mutation: Dilemma for diagnosis

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Introduction: Isolated hypoaldosteronism is a rare endocrinopathy in a limited number of patients who secrete normal level of cortisol, due to mutation in CYP11B2. In some cases clinical diagnosis can be late and genetic analysis showed difficulties.

Case 1: A 7 month-old girl infant was referred to endocrinology department due to vomiting, failure to thrive and severe hyponatremia with unexplained neutropenia. She was born term with 2440 gr. There was no consanguinity between parents. In her physical examination height, weight, relative body mass index were <-2 SDS. She had atopic eczema. In laboratory evaluation; we detected low Na (122 mmol/L), high potassium (5.9 mmol/L) and calcium (11.7 ng/dl) with high plasma renin activity (80.5 ng/ml/hours) and low aldosterone (13.3 pg/ml) level. NaCl and fludrocortisone was initiated. LC/LCMS revealed appropriate serum hormon profile with AS deficiency. A heterozygous change in the CYP11B2 (c.554 C>T (p.T185I)) was detected.

Case 2: A 2 month-old male infant was referred to endocrinology department due to severe hyponatremia with suspected diagnosis of congenital adrenal hyperplasia. He was full term, birth weight of 2700 gr. Parents were first degree cousin. In his examination, disseminate squamatos lesion was noticed. He was followed by immunolgy department for severe eczema, protein-losing diarrhea and eosinophilia in the mean time. His weight (3190 gr) height (52 cm) and head circumstance (35.5 cm) was <-2 SDS. While Na level was 124 mmol/l, PRA was high (100ng/ml/h) with low aldosterone level (5.4 pg/ml). LC/LCMS was compatible with diagnosis. A heterozygous change was detected in the CYP11B2 gene c.763 G>T (p.Glu255Ter).

In both infants, although mutations do not explain the etiology, it is thought that there may be an additional mutation in a region that affects gene function and that our cases may have compound heterozygous mutations. Because of the additional findings; neutropenia in Case 1 and eosinophilia in Case 2, advanced genetic analysis for Whole Exom Sequencing are carried on.

Conclusion: Aldosterone synthetase deficiency is a rare cause of persistent hyponatremia. Clinical findings vary with age. The association of eosinophilia and neutropenia has not been reported so far. In order to explain for these rare associations, an advanced genetic analyses is needed in rare cases such ours.

P3-9

Late onset 11 Beta Hydroxylase Deficiency: Two cases

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Introduction: Differential diagnosis should include congenital adrenal hyperplasia (CAH) in premature adrenarche patients. Clinically, it is possible to diagnose late onset and simple virilisation CAH caused by 21 hydroxylase deficiency because the criteria are

better defined and genetic tests are widely available. But especially late onset 11 Beta hydroxylase deficiency can be very difficult to diagnose because the diagnostic criteria are not well defined and genetic tests are not available for this rare type of CAH. Hereby we present two patients with premature adrenarche who were diagnosed with late onset 11 β HE.

Cases: General information on cases, symptoms, physical examination, laboratory and genetic results are given in Table 1.

Discussion and result: Prevalence of late onset 11 β HE among premature adrenarche patients is not known in our country. Ten to twenty times increases in stimulation tests should be carefully evaluated and diagnostic work up should include genetic confirmation when necessary. Diagnostic criteria will be reached by this way.

	Case 1	Case 2
Age/gender	7 years 9 mo-female	6,5 years-female
Birth weight (gram)-maturity	3250 g-term	3450 g-term
Symptoms and duration	Axillary hair, adult type sweat-2 months	Pubic hair-1 month
Height -cm (SDS)	128,3 (0,14)	121,6 (0,53)
Genitourinary system ve secondary sex characteristics	T1P1 AK + no cliteromegaly	T1P2 AK + no cliteromegaly
Bone age	8 years 10 mo	8 years 10 mo
DHEASO4 (0-45 µg/dl)	121,9	152,9
Total testosterone (0-40 ng/dl)	25	52
Basal 17 hydroxysprogesterone (0-1,5 ng/ml)	0,086	0,21
Stimulated 17 hydroxysprogesterone (0-1,5 ng/ml)	0,3	0,96
Basal 11 deoxycortisol (0-344 ng/dl)	22,6	40,1
Stimulated 11 deoxycortisol (0-344ng/dl)	499	806
Mutation (CYP11β1)	Exon 1-R43Q Exon 7-A386V Compound heterozygote	Exon 1-R43Q Exon 7-A386V Compound heterozygote
hypertension	No	No
Treatment	Hydrocortisone (7,5 mg/m ² /day)	Hydrocortisone (7,5 mg/m ² /day)

P3-10

An unusual Testicular Adrenal Rest Tumor localization in a 15-year-old boy with congenital adrenal hyperplasia

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Introduction: Testicular adrenal rest tumor (TART) is the most important cause of infertility in male with congenital adrenal hyperplasia (CAH). TART is a benign tumor, mainly bilateral (75-80%), usually diagnosed in under-treated CAH male with hypercorticotropinemia, which generally regresses after glucocorticoids therapy adjustment. However, it may determine an irreversible damage by compression and toxic-paracrine effects on the surrounding testicular tissue.

At ultrasound (US) examination, TART appears as hypoechoic, clearly delineated, rich and regular in vascularization, testicular lesions usually localized close or inside the testicular hilum.

We report the first documented case of unusual epididymal localization of TART in an adolescent with salt-wasting (SW) CAH.

Case Report: A 15-year-old Caucasian boy was diagnosed with SW CAH (Intron-2-splice mutation and 8-bp-deletion) because of an adrenal crisis at the age of 1 month. He was regularly followed up through biochemical tests and testicular US evaluations and treated lifelong with hydrocortisone and fludrocortisone acetate until the age of 14 when a progressive deterioration of disease control due to lack of compliance to therapy was reported. At the age of 15, scrotal US examination, demonstrated, for the first time, multiple, homogeneous and well-circumscribed hypoechoic lesions impairing both testes ranging between 3 mm to 7 mm, most of them located along mediastinum testis, and two other nodular lesions in both epididymis heads, the greater of which measuring 6 mm in size in the right one. Testicular and epididymal lesions showed increased intra and perilesional vascularization, associated with regular and linear caliber of the vessels coursing through the lesions at power Doppler evaluation, higher stiffness values compared to testicular parenchyma at strain elastography (SE) assessment, and low intensity signal in the T2 Weighted MRI images.

Conclusions: This is the first documented case of epididymal localization of TART in an adolescent with SW CAH. The diagnosis of TART should be always considered in CAH male with testicular lesions and an epididymal localization should be encountered. In those patients, testicular US screening should be performed regularly, at least every two years in early childhood and annually in the peripubertal period, or even more frequently in patients with lack of compliance to glucocorticoids therapy, even in absence of suggestive symptoms.

P3-11

Primary Adrenal insufficiency in Sudanese children (clinical presentation, etiology and diagnostic challenges)

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Introduction: Primary adrenal insufficiency (PAI), though uncommon, is a condition with a high morbidity and mortality especially in children where presentation may vary and mimic many common childhood illnesses. Many etiologies have been reported worldwide of which CAH was the commonest etiology in children. There is no published data on PAI in Sudanese children and to my knowledge, this is the first report in Africa that looks for clinical presentation and etiology of non-CAH (PAI) in children. We aimed to determine the clinical features at presentation, etiology and diagnostic challenges of PAI in children in a limited resource country like Sudan.

Methods: Descriptive, retrospective, hospital based study, was carried out in two major pediatric endocrinology centers in Khartoum state, Sudan from January 2006 to December 2018. Patient's records were reviewed (both in and out patient). All patients who have CAH as a known etiology were excluded. Clinical features at presentation as well as the possible etiology were described and difficulties encountered in the diagnosis, availability of certain investigations and their costs as well as barriers of management and availability of certain medications were addressed.

Results: In a total of ninety-seven patient's records who were referred as suspected PAI, sixty-four patients met the inclusion criteria for diagnosis of which 40 were males and 24 were females. Median age at presentation was 6.27 ± 4.41 years (range: 0.02 to 17 years). Symptoms at presentation included hyperpigmentation, fatigability, abdominal pain, diarrhea, vomiting, seizures and shock. Duration of symptoms before first presentation varied and 50% had wrong diagnosis at first presentation. We were able to determine a diagnosis in 39 (61%) patients of whom 26 were Allgrove syndrome, seven were ALD and 17 patients had possible autoimmune etiology. Diagnosis was difficult to be settled in 13 patients who need a genetic testing. Mean adrenocorticotrophic hormone (ACTH) at diagnosis was $(2185 \pm 2172 \text{ pg/ml})$. Four patients had elevation of very long chain fatty acids, while 2 had MRI abnormalities suggestive of ALD. Most of these investigations were costly while many patients have difficulty to access lifesaving medications.

Conclusions: Symptoms of increased pigmentation, lethargy, hypotension or electrolyte abnormalities, although unspecific and similar to many other childhood illnesses, yet should lead to consider this diagnosis as early intervention could further alter the outcome. Increasing awareness among pediatricians and accessibility to molecular genetics through help, have helped in diagnosing some of these cases.

P3-12**Clinical follow-up of a novel NR0B1 mutation in a case of Adrenal Hypoplasia Congenital**

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We have examined a male child patient aged about 15 years old to confirm the diagnosis of adrenal hypoplasia congenital (AHC) at the Genetics in-patient department, Children's Hospital Affiliated to Zhengzhou University. When the child was 5 years and 9 months, he was diagnosed as abnormal phenotypic characteristics who had skin hyperpigmentation, penis enlargement, rapid growth over the past 2 years, along with fatigue, drowsiness, and pubic hair appearing for 2 months. Based on the child's clinical manifestation, especially precocious puberty, primary adrenal insufficiency during the early stages, the child was misdiagnosed with 21-hydroxylase deficiency. However, the next generation sequencing performed on the isolated peripheral blood-DNA samples of the patient has confirmed the novel missense mutation with the heterozygous c.1411T>C (p.X471Q) occurred at the NR0B1 gene exon 2. This novel NR0B1 gene mutation was also confirmed by the Sangers DNA sequencing. Furthermore, a follow-up of the patient's clinical manifestations and laboratory examinations have confirmed the incidence of AHC, a X-link recessive genetic disorder in the patient. But because of the lack of regular clinic follow-up and medication, the patient had only grown to a height (156cm) that is far below his genetic target height (175.5cm). Also testicular dysplasia happened on the boy, so he has developed self-inferiority that directly affects his quality of life. Because the mutation of NR0B1 gene can lead to a wide range of clinical phenotypes, besides the classic type of primary adrenal insufficiency, low gonadotropin-related sexual dysplasia, and impaired spermatogenesis etc., the clinical phenotypes can also be precocious puberty, especially in infants and young children. The difference between NR0B1-related AHC and 21-OHD should be noted and early treatment and regular follow-up are essential for clinical outcome.

P3-13**Genotype and phenotype, growth outcome in 33 Korean patients with 21-hydroxylase deficiency**

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Purpose: This study aimed to describe gene mutations and growth outcome in patients with 21-hydroxylase deficiency

Methods: Subjects were diagnosed as 21-hydroxylase deficiency by direct Sanger sequencing or multiple ligation-dependent probe amplification analysis and visited Pusan National University Children's Hospital from July 2008 to April 2019. We investigated the genotype, phenotype and growth profiles.

Results: Among 33 patients with congenital adrenal hyperplasia (CAH), 17 were females and 16 were males. Median age was 7.7years (1month-23.8yr). Twenty-seven (81.8%) had salt-wasting phenotype. Fourteen (42.4%) initially presented with 17 OHP elevation, with no other symptoms. Among 17 girls, thirteen (76.5%) had ambiguous genitalia and 7 (41.2%) received genitalia surgery. We evaluated 66 alleles from 33 patients. The distribution of 21-hydroxylase deficiency gene mutations revealed that intron 2 splice site (c.293-13A/C>G) mutation was the most common (31.8%) followed by large/complete deletion (16.7%), and c.518T>A (15.2%), respectively. Three novel mutations (p.G111fs, p.Q319*, and homozygous complete deletion in CYP21A2 were detected. Ten (30.3%) needed growth hormone therapy due to short stature. Nine (47.4%) had bone age advanced more than 2 years. Five (15.2%) were treated for precocious puberty. Among 27 patients aged>2years, more than half (55.6%) were obese/overweight. When divided into two groups according to steroid dose(13.2mg/m²), more proportion of higher steroid dose group received growth hormone therapy than lower dose group(6.3% vs 52.9%, p=0.007).

Conclusion: Three novel and one recurrent (c.293-13A/C>G) CYP21A2 mutations were identified. Careful monitoring of growth profile is needed for CAH patients, especially in those with high steroid dose.

P3-14**One case report of Uighur girl with Cushing syndrome**

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Objective: Through the diagnosis and treatment of Uighur girl with adrenocortical adenoma, who was complain of short stature, to prompt pediatric endocrinologists pay attention to hypercortisolism in the diagnosis and treatment of children with short stature.

Methods: With the case report of hypercortisolism in a Uighur child, to introduce the diagnosis and treatment of adrenocortical adenoma, presenting the clinical characteristics of hypercortisolism in pediatric patient

Results: A 3.5-year-old Uighur girl complained of short stature and unable to walk at clinic. Six months after birth, she could sit stable. But after that, she had motor retardation and could not walk all the way. Her brothers and sisters are in good health. Physical examination: height 72 cm, body weight 10 kg, blood pressure 180/120 mmHg, central obesity, moon face, buffalo back, hypertrichosis, no obvious purple and white striae, breast Tanner stage I, muscle tension were normal, pubic hair Tanner stage III. Laboratory examination: serum potassium 2.5mmol/l, sex hormone: LH 0.29miu/ml, FSH 2.00miu/ml, testosterone 0.31ng/ml, estradiol 14.9pg/ml, progesterone 1.50ng/ml, cortisol 33.41ug/dl, ACTH 5.30pg/ml, aldosterone 121.88pg/ml, normal thyroid function

and blood gas analysis . Adrenal ultrasound: there was a goiter in right adrenal gland area, 30×19 mm, with irregular dark area. She had the typical manifestations of hypercortisolism, elevated blood cortisol, decreased ACTH with abnormal rhythm. Clinical diagnosis was confirmed of primary hypercortisolism due to right adrenal cortical tumor. Her short stature and inability to walk all due to hypercortisolism. After corrected electrolyte disturbance and antihypertensive treatment, she underwent surgery with complete resection of right adrenal tumors by urologist. Postoperative pathological reported adrenocortical adenoma. She had glucocorticoid replacement therapy after operation. Four months later, hormones and antihypertensive drugs were reduced gradually and stopped finally. Her height was increased by 3 cm. She could stand alone and walk. Blood cortisol 1.05 ug/dl, ACTH 4.77 pg/ml, serum potassium 4.9 mmol/l, blood pressure 85/60 mmHg, height 75 cm, weight 11 kg, body shape appeared normal, without moon face, hairs significantly reduced, pubic hairs alleviated. she was completely recovered after her first visit at my clinic 4 month later.

Conclusion: Cushing syndrome caused by adrenocortical adenoma can occur in infants and young children, with typical clinical manifestations of hypercortisolism, accompanied by short stature and motor retardation. The growth and motor development improved significantly after surgical resection. The prognosis of adrenocortical adenoma in younger child was satisfied.

P3-15

Nephrotic Syndrome Developed in a Girl With Lipoid Adrenal Hyperplasia due to StAR gene mutation – First Report

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Introduction: The incidence of idiopathic nephrotic syndrome (NS) is 1.5~16.9 per 100,000 children. The cause remains unknown but the pathogenesis of idiopathic NS is thought to involve immune dysregulation, systemic circulating factors, or inherited structural abnormalities of the podocyte. NS is characterized by the triad of proteinuria, hypoalbuminemia, and edema. There can be an antecedent infection, typically of the upper respiratory tract. Moreover, NS can be accompanied with several complications such as infection, thromboembolism and hypovolemic crisis. Here, we report a nephrotic syndrome with hypotension occurring in 10 years old girl with primary adrenal insufficiency

Case: A 10-years old girl was admitted in intensive care unit with generalized edema and mental change. She was the first baby (birth weight, 3.0kg, full term) of non-consanguineous parents. She had been diagnosed and taking medications (hydrocortisone, fludrocortisone) with primary adrenal insufficiency. She got fever 2 days before admission, and revealed generalized edema and mental change on the day of admission. She was diagnosed with idiopathic nephrotic syndrome two years ago.

The patient had a decreased blood pressure of 90/40 mmHg and tachycardia. The laboratory investigation results upon admission

were as follows: leukocyte count, 10,770/ μ L; platelet count, 341K/ μ L; hemoglobin level, 12.7 g/dL; sodium 129 mg/dL, potassium 5.3 mg/dL; BUN level, 18.0 mg/dL; serum creatinine level, 0.8 mg/dL; total protein 3.7 mg/dL; and serum albumin 1.59 mg/dL. Urinalysis showed protein (++++) by dipstick and nephrotic-range proteinuria (247.5 mg/m²/h)

The patient was diagnosed with idiopathic nephrotic syndrome, and adrenal crisis. She was initially treated with high dose intravenous hydrocortisone (100mg a day) due to adrenal crisis. Her hypotension and mental change were recovered on the second day of hospitalization, and then, the treatment was changed intravenous hydrocortisone into oral prednisolone. Remission of proteinuria was achieved after 8 days. To this day, the patient has been followed up for 10 months with remission

Conclusion: It is difficult to know whether two diseases have occurred accidentally or not. It was thought although both NS and adrenal crisis could contribute to hypotension and mental change of the patient, adrenal crisis mainly affected her condition at first. We first report an idiopathic nephrotic syndrome presenting hypotension and mental change, needed with high dose intravenous hydrocortisone developed in patient with lipoid adrenal hyperplasia.

P3-16

Pneumocystis Jiroveci pneumonitis complicating neonatal Cushing's syndrome - the therapeutic dilemma

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Background: Endogenous Neonatal Cushing's syndrome (CS) is a rare condition with around 100 cases reported worldwide. Pneumocystis Jiroveci pneumonitis (PJP) is a well described, albeit rare, complication of exogenous CS (i.e. CS resulting from external glucocorticoids). The pneumonitis usually occurs following reduction of glucocorticoid dosage and is therefore thought to be triggered by an inappropriate immune reaction evident after glucocorticoids withdrawal, treatment of which includes both antibiotics and glucocorticoids. PJP has not been hitherto described in neonatal endogenous CS.

Objective: To describe the problems associated with therapy of life-threatening PJP in a baby with active neonatal CS with particular attention to glucocorticoid levels.

Case Presentation: A 3-month old female infant presented with failure of linear growth and mild hirsutism. She was diagnosed with CS, with high fasting cortisol levels (893 nmol/l). After low dose (15 mcg/kg) dexamethasone- cortisol paradoxically increased to 1350 nmol/l- consistent with micronodular adrenal disease. Adrenal size was normal for age by computerized tomography. Within days of diagnosis of CS, she developed hypoxemia and severe respiratory distress requiring mechanical ventilation. A

chest x-ray typical of severe pneumonitis provoked performance of a broncho alveolar lavage by which Pneumocystis Jiroveci infection was diagnosed.

In order to prevent further exacerbation of pneumonitis, treatment of the CS was postponed and corticosteroids were administered. Despite antibiotic and steroid treatment and maximum mechanical ventilatory therapy, the baby's pulmonary status continued to deteriorate. Extracorporeal membranous oxygenation (ECMO) was commenced a week after the diagnosis of PJP pneumonitis. The combined antibiotics and glucocorticoids treatment was associated with successful eradication of PJP from bronchioalveolar lavage fluid but also with an increase in cortisol levels to above 3000 nmol/l (probably part of her paradoxical response to external glucocorticoids) and hypokalemia and hypertension appeared. Therefore, combined therapy with Ethomidate (0.15 mg/kg/h) and Metyrapone (50mg*6/d) was initiated and cortisol levels were successfully titrated to approximate expected stress levels of 700-1000 nmol/l. However, the pulmonary damage was irreversible and after 97 days on ECMO The infant died.

Conclusion: PJP complicating endogenous CS is a severe life-threatening condition. It is not clear how best to take care of glucocorticoid levels during therapy. This case shows that despite early diagnosis of both CS and PJP, outcome can be fatal. We present this case with the hope that accumulation of experience of this condition may help develop a successful therapeutic strategy for future cases.

life (8 nmol/l).He was a first-born from unrelated parents without significant illnesses. Pregnancy and vital parameters at birth were regular; birth weight was 3660 g. Due to the clinical picture and blood tests (basal 17OHP 158 ng/ml, renin 303.6 mUI/l -n.v. 2.8-39-, aldosterone 453 ng/l -n.v. 12-240-, normal sodium and potassium levels, LH peak after GnRH test 5.3 UI/l, FSH peak 1.9 UI/l), a diagnosis of classical CAH complicated by a central precocious puberty was made. Replacement therapy with hydrocortisone and fludrocortisone and puberty blocking therapy were started, with good clinical response. Treatment with human GH was also started to improve height prognosis. From the molecular investigation of the CYP21A2 gene, the patient resulted hemizygous for the p.l173N variant.

Discussion: Newborn screening has still limitations in the diagnosis of CAH. FN are produced for reasons still unclear including issues in timing and/or sensibility of laboratory tests. FN are underestimated, also due to the lack of an effective reporting system for patients with late diagnoses; furthermore, they are underreported in literature (Votava et al,2005; Schreiner et al,2008; Sarafoglou et al,2012). Therefore, pediatricians should be aware that a negative newborn screening does not rule out the manifestation of classical CAH during later stages of life.

P3-18

The unusual adverse side effects of super-potent topical steroids

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Background: Topical steroids are commonly used in clinical practice for management of dermatological diseases. Clobetasol propionate is the most potent. They are systemically absorbed and may cause adverse side effects due to improper and prolonged use, such as iatrogenic Cushing's syndrome and adrenal insufficiency due to suppression of hypothalamic-pituitary-adrenal axis.

Case Presentation: A 7-month-old boy referred to our Endocrinology unit in Alexandria University Children's hospital with obesity and oral thrush.

He had a history of diaper dermatitis of 2 months duration. During this period, his mother used Dermovate and Emovate cream (clobetasol propionate 0.05%) upon recommendations of a pharmacist. It was used 4-5 times daily all over the body and finished a tube every 3 days.

Mother noticed rapid weight gain of 4.5 Kg over 2 months and noticed that diaper dermatitis was not improving, so she stopped creams 2 weeks before presenting to us.

On physical examination, he had a cushingoid appearance with moon face, extensive oral thrush, hypertrichosis on his forehead, truncal obesity, buffalo hump and diaper dermatitis. His weight was 9.5kg (75th percentile), his length was 68cm (25th-50th percentile).

Despite that clobetasol cream had been stopped, he was hypertensive (blood pressure 140/90), and angiotensin-converting enzyme inhibitor (ACEI) was started.

His laboratory investigations showed mild hypercalcemia and hypercholesterolemia. Basal morning serum cortisol level and ACTH were low.

P3-17

Newborn screening for congenital adrenal hyperplasia: should we worry more about false positives or false negatives?

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Background: Newborn screening for congenital adrenal hyperplasia (CAH) is based on the determination of 17-hydroxyprogesterone (17OHP) on blood and its need is confirmed by the most recent guidelines on the subject. In Italy this screening is not mandatory, and its application is on a regional basis. Among its disadvantages, it is well known the high frequency of false-positives, in particular in premature babies and those born small for gestational age. However, there are a number of subjects who are false-negatives (FN), with the risk of late diagnosis and development of complications.

Case Report: A 4-year-old boy presented with pubic hair, body odor and acne noted one year earlier. At clinical examination, height was 125.1 cm (+3.85 SDS, target height +0.70 SDS), weight 25.1 kg (+2 SDS) and he had mild acne in his face. He was Tanner stage 2 (G2PH3, testicular volume 4 ml bilaterally). Bone age was 12-13 years. In his previous medical history, he was recalled for CAH screening performed at 3 days of life (17OHP 35 nmol/l, n.v.<18), showing normal values of 17OHP at 6 days of

Echocardiogram revealed mild left ventricular hypertrophy, likely due to hypertension, despite the short duration of topical steroid use. Sonography of adrenal glands and kidneys was normal.

Intravenous stress dose hydrocortisone and diflucan were given, serum total calcium normalized and oral thrush improved.

Hypercalcemia was interpreted to be induced by adrenal insufficiency, which occurred due to the abrupt stoppage of clobetasol cream. This was confirmed by normalization of serum calcium level by only administering steroids.

Then the patient was shifted to physiological dose of prednisolone, with a plan for gradual tapering. On follow up, weight decreased, calcium levels remained normal, and ACEI dose was stopped.

Conclusions: Over-the-counter availability of super-potent topical steroids has led to their misuse or overuse causing iatrogenic Cushing syndrome. Lower-potency agents are preferred in infancy, with limited duration and dosage, under-supervision of a physician.

Abrupt withdrawal of topical steroids without seeking medical advice can lead to adrenal insufficiency, which can cause hypercalcemia. Hypertension can occur and may persist even after cessation of use. Therefore, measuring blood pressure and screening those patients with echocardiogram and serum calcium is recommended.

P3-19

A case with central adrenal insufficiency and early onset obesity: Proopiomelanocortin deficiency

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Introduction: Proopiomelanocortin (POMC) deficiency is a rare disease characterized by central adrenal insufficiency, early-onset obesity, red hair, and impaired skin pigmentation. This disease is caused by mutations of *POMC* that is localized in 2p23.3. Here, we aimed to present a case with central adrenal insufficiency, red hair, and rapid weight gain and who was detected frameshift mutation in the *POMC*.

Case: A 16-day-old girl was brought to our hospital due to poor feeding and jaundice. Her past medical history revealed that she was born after the first and uneventful pregnancy of a mother with a birth weight of 3270 grams at 41 gestation weeks. Family history was unremarkable and the parents were no relatives. On physical examination, weight was 3030 g (-1.29 SDS), height was 50.6 cm (-0.17 SDS), head circumference was 35.8 cm (0.14 SDS), and also icteric appearance and red hair were observed. Genital examination revealed normal female external genitalia. On the laboratory, hypoglycemia (30 mg / dL), mild hyponatremia, negative urine ketones; high serum levels of total bilirubin, ALT / AST, and elevated ammonia-lactate were found. Serum acyl/carnitine profile was in

the normal range. Hormonal profile revealed free T4 1.14 ng / dL, TSH 9.01 U / L, FSH 0.57 U / L (0.1-3.3), LH 0.24 U / L (0-1.9), DHEA-S 4.7 µg/dL, prolactin 18.5 mIU / L (3-24), serum insulin 0.32 U / L, cortisol 0.08 µg/dL, ACTH <5 pg / mL. The peak cortisol response was inadequate in the low-dose ACTH test (11.2 µg/dL). Pituitary MRI was normal. Central (secondary) adrenal insufficiency was established and 10 mg / m² hydrocortisone treatment was started. Red hair and central adrenal insufficiency were suggestive for the diagnosis of POMC deficiency and following genetic analysis, a homozygous mutation in the *POMC* [c.206delC (p.P69Lfs*2)] was detected. Hypoglycemia was not recorded after hydrocortisone treatment, and progressive weight gain was observed during the follow-up. At the most recent follow-up when she was at the age of three years and 10 months, weight was 23.2 kg (3.07 SDS), height was 101.2 cm (0.31 SDS) and body mass index was 22.7 kg / m² (3.58 SDS). She was on treatment with hydrocortisone (6.8 mg / m² / day).

In Conclusion: In cases with central adrenal insufficiency, red-hair, and early-onset obesity, POMC deficiency should be suspected and molecular genetic confirmation by analyzing of *POMC* should be performed.

P3-20

Short Synacthen Test in Children at Sultan Qaboos University Hospital; Reviewing the sampling times

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Introduction: Primary adrenal insufficiency in paediatrics is uncommon but lethal condition, it results most commonly from congenital adrenal hyperplasia¹. Short Synacthen Test (SST) is widely used to assess the glucocorticoid synthesis in the adrenal glands. Synacthen doses are age-based; 62.5mcg for babies younger than 6months, 125mcg for infants between 6-24 months and 250mcg for children older than 2years. There is a controversy amongst endocrinologists about the necessity of sampling at 30min^{2,3}. 0 and 60min samples are claimed to be sufficient for a diagnostic SST result.

Aim: To Report our experience and review the SST protocol in patients investigated for primary adrenal insufficiency with a focus on the concordance between 30 and 60min serum cortisol(SC) measurements.

Methods: All SSTs were performed in our Biochemistry Laboratory were reviewed for paediatric endocrine patients aged below 16 years old between 01/01/2014 to 31/12/2018. The cut off used for SC value is 550 nmol/L.

Results: 53 SSTs (43 patients;F23) were identified via Hospital Information System database and day care unit registry. Mean age and standard deviation were 6±5 years, ranged between 3days and 16years. Out of 53 performed SSTs, only 15 SSTs included the 30min sampling, whereas the rest were done by measuring SC at 0 and 60min. t-test showed difference in the average SC level between 30 and 60min (p 0.0017). The mean SC at 30min was 597nmol/L and 750nmol/L at 60min respectively. In 2 occasions the peak SC was recorded highest at 30min with 6 and 37nmol/L

difference in values. Howbeit, it did not lead to change of management should we relied on the 60min reading for those 2occasions. The SC was 48nmol/L for one patient and 684nmol/L for the other i.e. there was clear fail or pass of the SST.

For the rest of performed 38SSTs; sampling was done at only 0 and 60min. There was no dilemma in interpreting results based on their 60min SC readings. It was above 550nmol/L in 24 occasions and below 500nmol/L in other 13 occasions. Only 1 patient had a peak of 512nmol/L which warrant repeating a test to include 30min sampling in case the peak could be higher at this time.

Conclusion: Higher SC levels at 60min compared to 30min was observed; therefore, 30min sampling is not recommended. This may contribute to patient comfort, reducing cost and workload. If peak SC in range of (500-550pmol/L) then consider repeating the SST by including the 30min sampling.

P3-21

Pheochromocytoma in children: a case report

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Pheochromocytoma (PCC) is a rare tumor arising from the adrenal medulla as well as extra-adrenal paraganglion system and secreting catecholamines causing severe hypertension in children. The gold standard for diagnosis is the measurement of free plasma levels of metanephrenes while management evaluates the location and size of the tumor and possible metastatic lesions. Preoperative treatment with alpha blockers, beta blockers and tyrosine hydroxylase inhibitors improves safety of the surgical procedure.

Objectives: To describe the clinical characteristics, investigation data and outcome of patients with PCC.

Subjects and Methods: this is case study including clinical symptom descriptions, biochemical and imaging investigations, and management for two children with PCC.

Results: The female patient was 7 years old, with no medical history. She presented with vomiting, headache, abdominal pain and convulsions. Blood pressure was 220/190 mmHg and heart rate 130 / min on admission. Abdominal CT showed a left adrenal tumor of 24x25 mm in size. Plasma level of cortisol and noradrenaline were 1374 nmol / L and 971 pg / ml, respectively; and urinary HVA level was 7.8 µmol/mmol of creatinine. Preoperative blood pressure was controlled with nicaldipine, doxazosin mesylate and amlodipine. A 2x3 cm tumour was removed through endoscopy. After surgery, patient was stable with normal blood pressure.

Conclusions: PCC is the cause of treatable secondary hypertension. Stabilizing blood pressure prior to surgery, contributes to ensure surgical treatment safety. Multidisciplinary collaboration is warranted to optimize the management of patients.

P3-22

A Case with Congenital Adrenal Hyperplasia Diagnosed by Malnutrition

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Introduction: Congenital adrenal hyperplasia is an autosomal recessive disorder characterized by enzyme deficiencies in the adrenal steroidogenesis pathway. The most common type is 21 hydroxylase deficiency and is divided into two groups as classical and nonclassical type. 75% of the classical type of cases is salt-losing type, and cortisol and aldosterone deficiency symptoms occur in patients. Female cases presented with ambiguous genitalia due to hyperandrogenemia at birth. In male cases, scrotal hyperpigmentation and macropenis are present.

Case: A 7-month-old male patient was referred to us because of the high level of TSH in his examinations. His past medical history revealed that he was born with 3000 grams he did not have any complaints such as concomitant vomiting and diarrhea. It has been learned that the child has been followed up by the department of gastroenterology for developmental delay since 3 months. His parents are first degree cousins.

On his physical examination weight:4.7 kg (-3.92SD), height:62 cm (-2.61SD), he was malnourished, thyroid stage 0, axilla negative, pubis tanner stage1, testes 2/2 ml palpable bilateral in scrotum, penis length was 3 cm, there was no scrotal hyperpigmentation. In the laboratory the values: fT4: 1.01 ng/dl, TSH:10.5 uIU/ml, glucose: 75 mg/dl sodium: 127.9 mmol/L potassium:5.74 mmol/L were found. ACTH:41.8 pg/ml cortisol: 4.42 ug/dl, 17 OH progesterone > 19.2ng/ml, renin 2.59ng/ml/h, aldosterone 19.1ng/dl, the patient was hospitalized because of mineralocorticoid deficiency and the standard dose ACTH stimulation test was performed.

ACTH at baseline: 14.3 pg / ml, cortisol: 0.68,6g / dl, 17 OH progesterone: 2.26 ng/ml; peak cortisol: 1.47:g / dl, peak 17 Oh progesterone: 92.3 ng / ml. hydrocortisone 15 mg/m2/day, fludrocortisone 2x 0.1 mg and 3 gr/day oral salt treatment was started with diagnosis of adrenal insufficiency. In the genetic analysis, the CYP21A2 gene revealed a c.293-13C> G homozygous mutation previously described in the literature. The patient's parents were also shown to be carriers of the same mutation.

Conclusion: This case was diagnosed because of hyponatremia and hyperkalemia at 7 months of age due to malnutrition. There is no macropenis and scrotal hyperpigmentation in the clinic and there is no hypoglycemia and vomiting symptoms. The patient's basal ACTH was normal and this condition was thought to be related to malnutrition. This case is presented because of its late diagnosis and presentation to a different clinic.

P3-23

Recurrent Hypoglycemia-Not every low sugar is hyperinsulinemia

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Introduction: Recurrent hypoglycemia is a life threatening condition. And its early diagnosis and correct diagnosis can be crucial to entail survival of the child.

Objectives: To review this case with respect to the clinical scenario and critical pathways we should remember while investigating a case of recurrent hypoglycemia.

Methods: History-

A 5 year old, Pakistani origin, male child presented to the Pediatric endocrine clinic with chief complaint of recurrent hypoglycemia. Patient had presented to Emergency room with an episode of documented hypoglycemia(blood sugar 2.2 mmol/l).Patient was given some IV fluids, stabilised and sent home without any critical sample saved. There was past history of documented recurrent hypoglycemia associated with high fever, vomiting, diarrhea. There was also history of sweating episodes. Child was first born, product of non-consanguineous marriage, full term with average birth weight. There was history of neonatal intensive care stay for pneumonia and respiratory distress with h/o one episode of convulsion ?related with hypoglycemia. There was a positive history of diagnosed with Dextrocardia and Situs inversus. The patient had been apparently evaluated previously by Pediatricians at various hospitals locally and in their home country for hypoglycemia including extensively for hyperinsulinemia (but never correlated). The parents had been even given glucometer to keep a measure of glucose levels and instructions for taking sugar in case of hypoglycemia. He was also diagnosed as subclinical hypothyroid lately and had been prescribed thyroxine supplements. He had been also diagnosed with autism because of poor school performance and poor attention span.

Clinical examination -Anthropometry -Weight at 10th percentile and Height at 50th percentile.General examination revealed alert child with a sallow complexion, frequent eye blinking because of dry eyes, dark greyish discoloration of around gums. Mild to moderate development delay (predominant speech) was also noted. Rest of the systemic exam was normal other than the systemic finding related to situs inversus and dextrocardia.

The labs were ordered including fasting sugars, insulin and complete hormonal panel.The significant results showed ACTH of 425 pmol/l (1.6-13.9) and nearly undetectable cortisol levels at 0.5 nmol/L(171-536).CT scan adrenal showed relatively thinned out (possibly atrophic) adrenal glands with tiny right calcific focus with situs inversus totalis.

The child was diagnosed as a case of primary adrenocortical insufficiency and started immediately on age and body surface area appropriate dose of hydrocortisone. Further investigations,other relevant findings and management challenges for such a case will be discussed.

P3-24

Clinical characteristics and genetic analysis in one patient with congenital lipoid adrenal hyperplasia

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Objective: To explore the clinical and molecular genetic characteristics of congenital lipoid adrenal hyperplasia (CLAH), and to sequence the acute regulatory protein (steroid acute regulatory, StAR) gene of the infant patient and her pedigree.

Methods: Physical examination, laboratory tests, and imaging examination of the 1-month-old patient with CLAH were collected. DNA was extracted from blood samples of the patient and her parents. The 7 exons of StAR gene were amplified by PCR and then sequenced

Results: The main symptoms were low fever, vomiting, no weight gain, poor response, deep lip color, dark skin, girl vulva. The adrenocorticotropic hormone (ACTH) was above 2000pg/ml, cortisol was 14.1nmol/L at 8 am, 17-hydroxyprogesterone was 2 nmol/L, androgens levels was normal, serum sodium was 125-133mmol/L, serum potassium was 5.6-8.1mmol/L. Karyotype analysis showed 46,XX. Sequencing of PCR amplified fragments showed that there were one heterozygous mutations and another deletion c.544C>T(p.r182c), c.714del (NM_000349) of StAR gene in this patient. By rectifying the disturbance of electrolyte, and treating with hydrocortisone and 9α fludrocortisone, etc, the patient has been stable so far.

Conclusion: The chromosome and StAR gene should be detected in patients with primary adrenocortical dysfunction with low 17-hydroxyprogesterone and androgens, especially in female phenotypes. Children with lipoid adrenal hyperplasia can survive for a long time and grow normally after appropriate corticosteroid replacement therapy.

P3-25

Unusual association : Allgrove syndrome and hypopituitarism

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Introduction: Allgrove syndrome is a genetic disorder of autosomal recessive inheritance associating in its complete form: Esophageal achalasia; alacrymia and adrenal insufficiency. This is generally an adreno-corticotrophic hormone (ACTH) resistant. In this context we report the case of a patient followed in the endocrinology department.

Case: This is the case of a boy who comes from a consanguineous marriage, with family history of hypogonadotropic hypogonadism in one sister. Its history goes back to the age of 2 years by

the discovery of a micropenis associated with bilateral cryptorchidism, where the diagnosis of hypogonadotropic hypogonadism was retained and the patient benefited orchidopexy and hormone replacement therapy and an alacrymia for which he is put under artificial tears. At the age of 22, he developed an adrenal insufficiency confirmed by a low level of serum cortisol contrasting with ACTH raised to 90 pg / ml. For a few years he has been reporting the notion of dysphagia and in front of the association of an alacrymia and addison's disease the diagnosis of allgrove has been strongly suspected and the patient has benefited from a genetic investigation.

The result of molecular analysis has revealed the majority mutation in the homozygous state (IVS14 + 1G → A) by targeted molecular analysis of the AAAS gene, confirms the diagnosis of Allgrove in our patient.

Conclusion: Allgrove syndrome is a rare pediatric disorder, associating alacrymia and achalasia that are constant and early, and a less constant adrenal insufficiency. These disorders are at the origin of an alteration of the quality of life of the patients imposing a multidisciplinary care and especially a genetic advice in the siblings.

P3-26

Title: Long-term outcome of congenital adrenal hyperplasia patients at KFSHRC-Saudi Arabia.

Tertiary Center Experience

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Background: Congenital adrenal hyperplasia (CAH) refers to a group of inherited genetic disorders involving deficiencies in enzymes that convert cholesterol to cortisol within the adrenal cortex. Deficiency of 21-hydroxylase is the most commonly defective enzyme. Affecting 1 of 8000 live births in KSA. It requires life-long steroid replacement therapy in form of glucocorticoid and mineralocorticoid replacement. Without appropriate monitoring, 21-OH deficiency may result in significant complications either from over or under replacement.

We have the privilege at KFSH-RC, Riyadh to follow a large cohort of patients with CAH. To the best of our knowledge there is no available published data from Middle East about the impact of CAH on adult patients.

The aim of our study is to assess the health status of adolescent and adults with 21-hydroxylase deficiency and the need for changes in current management of pediatric patients and to emphasize the importance for endocrine specialist care as adult.

Methodology: It is a retrospective study. We reviewed medical files of all 21 hydroxylase deficiency cases still undergoing follow-up checks in our clinics and who are above the age of 14 years. All clinical, biochemical, and genetic data were collected.

Results: Among the 101 patients involved in the study, 67% were females. Mean age for males is 16.84.6± (range: 15-30 years), while mean age for females is 20.37.2± (range: 15-41). All cases of 46 XX 21 that had ambiguous genitalia were raised as females except 2 patients raised as males. 52% of patients are on hydrocorti-

sone, 40% on prednisolone while 8% on dexamethasone. Only 60% of patients were compliant on therapy. 23% were severely short and 32% were obese. 15% had primary amenorrhea and 29% of male patients had adrenal rest tumors. 7% had hypertension. DM and dyslipidemia in 3% each. osteoporosis was present in 7%.

Conclusion: One third of our patients were short and obese and one third of ales had adrenal rest tumors. these were the most common complications that were related to poor compliance to treatment. Our data is comparable with data published from other centers of excellence. we recommend that these patients need to be followed by expert endocrinologist to treat these complications.

P3-27

A boy with adrenal hypoplasia congenita without external genital abnormalities

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Background: Adrenal hypoplasia congenita (AHC) is a rare disorder with an estimated frequency of 1 case per 12,500 live births. AHC causes 46,XY disorders in sex development (DSD) due to adrenal androgen deficiency.

Objective: Case report on a male AHC patient with no external genitalia abnormalities.

Case Report: The baby was born at 37 weeks' gestation with a height of 46.5 cm (-0.49SD), a weight of 2,175 g (-1.57SD), and a head circumference of 30.0 cm (-1.93SD). He had generalized pigmentation at birth. He was discharged without any problems five days after birth and only required daily light therapy. However, he was referred to a hospital at 11 days old due to poor feeding and poor weight gain. He was not thriving and had peripheral circulatory failure. Laboratory data showed low serum sodium (134 mEq/L) and high potassium (7.1 mEq/L) levels. He had suspected adrenal insufficiency and was transferred to our hospital for close investigation. He displayed pigmentation, particularly in the lips, areola, and vulva. His external genitalia were completely male, with no micropenis, hypospadias, or cryptorchidism. Ultrasound showed that his adrenal gland was smaller than normal size. Laboratory data showed normal cortisol levels (5.1 µg/dL) with high ACTH (1,078 pg/mL), high aldosterone (294.5 ng/dL), high renin (187.9 ng/mL/hr), low DHEA-S (4.1 µg/dL), and normal testosterone (55 ng/dL) levels. The ACTH test showed no response of cortisol (base 9.6 µg/dl, peak 8.2 µg/dl). We determined that his Δ5-steroids were decreased according to GC-MS measurements of urinary steroid hormones. He was diagnosed with AHC and began hydrocortisone and fludrocortisone. No NR0B1 mutations were detected by Sanger sequencing. An analysis of the causative gene is underway.

Discussion and Conclusion: We consider that his fetal adrenal gland secreted sufficient androgen for external genital

development; however, the development of his adult adrenal gland was impaired. When encountering a patient with pigmentation, we should consider AHC even if no external genital abnormalities are present.

Bone, Growth Plate and Mineral Metabolism

P3-28

Linear growth in Children with COW Milk allergy and their response to hypoallergenic diet; Significant Catch-up in the first 6 months

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Introduction: Milk allergy is an adverse immune reaction to proteins in cow's milk. Treatment consists of eliminating milk from the diet. Controversy exists about the effect of CMA and the use of hypoallergenic formula on linear growth in these children.

Objectives: To evaluate the growth status of children with CMA at their first presentation and after 6 months of hypoallergenic formula.

Material and Methods: An observational, longitudinal, retrospective study was done on all infants and children diagnosed with CMA and who had high serum IgE level diagnosed between 6-2016 and 12- 2017. The following data were analyzed: chronology and type of feeding, the presence of allergy to other foods, atopic dermatitis or other symptoms of allergy, duration of CMA, and anthropometric data (weight and height) at diagnosis, and follow up after 6 months. Anthropometric data were expressed as Z-scores.

Results: A total of 20 children aged between 2 months to 59 years, with a mean age = 1.34 +/- 1.9 years were studied. Allergy to foods other than milk was found in 35%. At first presentation their BMISDS = -0.12 +/- 1.3, with 3/20 had BMISDS < -1.5. Their Ht SDS = -0.68 +/- 1.057, with 4/20 children with HTSDS < -2. After 6 months of taking hypo-allergic formulae the BMISDS = -0.196 +/- 1.1 and only 1/20 children had BMISDS < -1.5. This child has a significant catch up in Ht SDS from -1.6 to -1.1 which explained the same BMISDS despite gaining weight properly. After hypoallergenic diet their Ht SDS = -0.497 +/- 0.97 only 1/20 who had multiple food allergies had Ht SDS < -2 with low weight gain (4.4 g/day during the treatment period).

Conclusions: Our study showed that 20% of children with CMA had short stature and 15% had low weight for height at presentation. Improvement of linear growth and weight gain was observed in these patients when put on hypo-allergenic formula. The rest of the children, with normal anthropometric data at presentation, continued to grow normally on a hypoallergenic diet. The presence of other food allergies might affect weight gain and linear growth in some children

P3-29

Extreme hypercalcaemia: Watch for glycogen storage disease type 1a with hyperinsulinism

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Background: Hypercalcaemia in infants may reach extreme levels due to hyperparathyroidism, subcutaneous fat necrosis, or vitamin D intoxication. Normal values for p-parathyroid hormone and p-calcitriol prompt search for other causes.

Methods: Hospital file evaluation, case report.

Results: A 5½-months-old Caucasian girl of non-consanguineous healthy parents was referred due to weight loss with escalating total p-calcium to 3.86 mmol/L, p-ionized calcium 1.85 mmol/L (pH corrected). P-parathyroid hormone was <0.4 pmol/L, p-25-hydroxyvitamin D₃ 93 nmol/L, calcitriol 60 pmol/L, urine calcium/creatinine ratio >6/0.9. Mild hypercalcaemia and transient elevation of ALT was noted months before. Emergency treatment included i.v. fluids, bisphosphonate, steroids, calcitonin and potassium citrate.

A rapidly increasing p-lactate to 21 mmol/L led to severe acidosis with respiratory exhaustion and intubation. Blood glucose was 3.9 mmol/l upon arrival, but non-ketotic severe hypoglycaemia (p-glucose 0.1 mmol/L) occurred the following day, promptly treated with i.v. glucose. Oral feeding was discontinued. Further evaluation showed severely enlarged, hyperechoic liver, increased p-ALT (127 U/L), GGT (202 U/L), p-triglycerides (10.4 mmol/L), LDL cholesterol (1.8 mmol/L) and p-pyruvate (230 mcmol/L at p-lactate 2.0 mmol/L); mildly enlarged kidneys with nephrocalcinosis grade 1-2; and urinary loss of potassium, magnesium, phosphate and albumin in addition to calcium, all requiring i.v. and/or oral substitution.

P-growth hormone and cortisol did not suggest hormone insufficiency. Urine metabolic screening showed severe ketosis; p-amino acids and acylcarnitine profile were normal for the dietary circumstances. A rapid trio whole exome scan identified compound heterozygous mutations (c.508C>T, p.Arg170Ter and c.562G>C, p.Gly188Arg) in G6PC, confirming the diagnosis of glycogen storage disease type 1a (GSD1a).

The i.v. glucose demand increased to 17.5 mg/kg/min at 12 days after admission, where a hypoglycaemia test showed inappropriately elevated p-insulin of 41 (ref. 18-173) pmol/L at p-glucose 3.0 mmol/L, p-C-peptide 1234 (ref. 400-1600) pmol/L, confirming hyperinsulinaemic hypoglycaemia.

The patient was referred to the national centre for GSDs. Dietary treatment with continuous tube feeding with soy-based formula, dextrose and i.v. glucose to keep p-glucose in the range of 5-7 mmol/L succeeded to control the hyperlactataemia. The i.v. glucose demand gradually decreased and bolus meals could be initiated.

Conclusion: GSD1a with metabolic crisis can lead to severe hypercalcaemia despite suppressed p-parathyroid hormone and normal p-calcitriol. Hyperinsulinaemic hypoglycaemia can complicate the treatment during the metabolic crisis.

P3-30

ENPP1 hypophosphatemic rickets in a 3.6 years old Italian child

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Introduction: Although vitamin D deficit is the most common cause of rickets there are many rare genetically transmitted forms as hypophosphatemic rickets, a family of hereditary diseases characterized by low phosphorous plasma levels and resistance to 25OH-vitamin D replacement.

Case Report: This is the case of a 3.6 year-old Italian child sent from the General Pediatrician, for rickets suspicion. Silent personal history and familiar anamnesis, no history of consanguinity.

The baby was breast-fed until she was 11 month-old and she was regularly supplemented with 25OH-vitamin D for 12 months after birth. Examination: 94.3 cm (25° centile, -1.25 SDS) ; 14.5 kg (25° centile, -0.69 SDS); TH 172 cm (75° centile,). Presence of rachitic rosary, bracelet and femoral bowing. Biochemical data at presentation: calcium 1.18 mmol / l (n.v. 2-2.6), phosphate 0.84 mmol / l (n.v 1.1-1.94), alkaline phosphatase 527 U / l (n.v. 150-380), PTH 52.7 pg / ml (n.v 9-65), 25-hydroxyvitamin D 16.7 ng / ml (n.v. >30), RTP 82% (n.v. 80-90). X ray lower limbs: bowing of femur with enlargement and structural irregularities of distal metaphyseal epiphyseal regions; similar features also present at the tibia level. Normocalcemia and normal levels of 25(OH)D (after three months of 25OH-vitamin D supplementation), combined with normal PTH values in presence of hypophosphatemia, suggested vitamin D resistant hypophosphatemic rickets. Although molecular analysis of PHEX gene didn't find any mutations, further genetic investigations have allowed to find two variants in heterozygous in the ENPP1 locus: the translocation c.715+2T>g in exon's 6 splicing site and the deletion c.1437+3_1437+6del4 in intron 14 (ARHR2), responsible for another rare autosomal-recessive form of the disease. The same mutations have been confirmed respectively in mother and father who are healthy genetic carriers.

The child has started treatment with the active vitamin D metabolite, 1,25(OH)2D pills 250 ng: 17.2 ng/kg/day, associated with inorganic phosphorous salts pills 195.6 mg : initial dose 26.9 ng/kg/day divided in 2-3 doses day. During the follow-up, a 2/6 systolic pulse has appeared, associated to a pathological echocardiogram showing calcification at the aortic valve. Moreover she has developed bilateral transmitting hypoacusia, lower limbs pain, fatigue and dental enamel disturbances.

Discussion: With current therapy based on supplementation of phosphate and 1,25(OH)2D complete healing of the osteomalacia and correction of the biochemical abnormalities are generally incomplete. Patients affected by hypophosphatemic rickets need to start a multidisciplinary follow-up including endocrinologist, orthopaedic, odontoiatric and cardiologist specialists.

P3-31

A case study of X-linked hypophosphataemia: The effect of conventional therapy from childhood to adulthood in Saudi Arabia

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X-linked hypophosphataemia (XLH) is the most common form of inherited hypophosphataemic rickets, caused by loss-of-function mutations in the gene encoding phosphate-regulating endopeptidase homologue X-linked (*PHEX*), resulting in excess circulating fibroblast growth factor 23 (FGF-23).^{1,2} In children, therapy includes daily oral phosphate and active vitamin D analogue (alfacalcidol or calcitriol) supplementation, but is associated with gastrointestinal side effects and hyperparathyroidism.² In adults who have undergone conventional therapy during childhood, but are still symptomatic, conventional treatment is usually maintained or re-initiated in order to reduce pain as a result of micro-fractures and/or osteomalacia; however, the side effects of conventional treatments persist.² Here we report the case of an adult patient with XLH and the impact of the side effects of conventional therapy since his diagnosis.

The patient was diagnosed with XLH at aged 4 years and had a history of leg bowing, which had previously resolved with treatment. At age 20, he presented with pain during walking. He had no hearing or dental issues or limb deformities and was being treated with oral phosphate supplementation (30–50 mg/kg t.i.d.) and alfacalcidol (1.5–3.0 µg q.d.). Whilst on conventional treatment, growth, leg deformities, dental health and serum levels of alkaline phosphatase (ALP), parathyroid hormone (PTH), calcium, and creatinine were monitored every 6 months, as were urine levels of calcium and creatinine. A renal ultrasound was performed every 12 months. The patient developed medullary nephrocalcinosis in his right kidney at age 9 and a large parathyroid adenoma at age 20 and was referred to a surgeon. Both findings were thought to be related to long-term conventional therapy with oral phosphate and alfacalcidol, so therapy was discontinued. Following treatment discontinuation, most recent serum levels were as follows: high ALP, 1622.6 U/L; high PTH, 1403.0 ng/L; low phosphate, 0.93 mmol/L and urine calcium/ creatinine ratio was 0.07.

In this adult case of XLH, long-term treatment with oral phosphate and vitamin D supplementation therapy since childhood has resulted in significant side effects. Therapies targeting the underlying pathophysiology of the disease, i.e. FGF23 excess, and with fewer side effects are desirable.

P3-32**A Chinese girl suffered both Osteogenesis Imperfecta and mucopolysaccharidosis: Trio WES could tell us more**

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Case: A 7-year-old female revealed short bowed femurs and humeri with old fractures and bowed tibias and fibulas. Her height was 97cm and weight was 11kg. Her younger sister had the same phenotype as same as her mother. The Trio WES test showed that they all inherited from their mother's COL1A2 gene mutation (c.928G>A; p.G328S) and diagnosed Osteogenesis Imperfecta, type IV. Unfortunately, the 7-year-old girl also presents coarse face, short neck, limited mobility of large and small joints, claw hands, pectus carinatum and blue sclera. Genetic testing revealed she had another compound heterozygous mutation (c.1855C>G, p.R619G; c.1422_1423dupCT) in IDUA gene, inherited from father and mother, respectively. And she was diagnosed mucopolysaccharidosis Ih.

Conclusion: Our case shows that the Trio WES could help clinical doctors to identify unexpected diagnosis of dual rare disease precisely. And remind doctors to realize the chance of more than one rare diseases could occur in one patient.

P3-33**In case of osteogenesis imperfecta transmission in pregnancy: check vitamin D and calcium status of the mother**

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Background: A one-month-old girl was referred to our unit for osteogenesis imperfecta (OI). She was the first child of non consanguineous parents. The father had no history of fracture. The mother, 28 years-old, presented with a severe OI, short adult height (140 cm), moderate scoliosis. She had more than 20 limb fractures, no vertebral fracture and bowing limbs without need of surgery. She received Bisphosphonates during 3 years until 12 years of age. Then she stopped any treatment and medical following in spite of a fracture occurring every year. During pregnancy, she received 100,000 units of 25-hydroxyvitamin D (25OHD), and had a low uncorrected calcium consumption (600 mg/day). At 33 weeks of gestational age, a femoral fracture occurred after a fall. She had an orthopedic management and a laboratory investigation. A vitamin D deficiency was noted. 25OHD level was 4 ng/ml. Vitamin D and calcium supplementation (1g/day) were started

with efficiency on laboratory results. The fetus presented signs of OI on the ultrasound: short and bowed long bones.

Neonatal Management: The girl was born at 37 weeks of gestational age by vaginal delivery, SGA with 1.7 kg weight, 37 cm height. Clinical examination and radiographs confirmed OI with bowing of long bones, blue sclera. She had plagiocephaly and an important defect of mineralization of the skull in occipital and fronto-parietal regions. Brain computed tomography confirmed that. 25OH vitamin D was low at birth. We supplemented it and optimized feeding. The first fracture occurred on 1 month, without any traumatism. We started treatment with Zoledronate Acid injection every 3 months. She is now 15 month-old, with the occurrence of 4 limb fractures and 2 vertebral fractures.

Conclusion: During pregnancy, the mother had vitamin D deficiency and lack of calcium intake. In our case, the impact on the mineralization of the fetus skeleton was severe, affecting the skull. In OI pregnant women, early checking and following of bone and phosphocalcic status, is required to optimize it early with supplementation. OI women should be informed of the risk of defects on mineralization of fetal skeleton and its consequences in case of vitamin D or calcium. Moreover, we should better explain to OI patients the issues of medical following and treatment in adulthood.

P3-34**Study of response to vitamin D replacement in North Korean refugee children and Korean children**

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Purpose: It is well known that obesity and nutritional status are related to vitamin D deficiency (VDD).

We investigated the response to vitamin D replacement in normal-weight and overweight children of Korean and North Korean refugee children.

Methods: This study was performed from 2011.1 to 2018.12. It was a prospective study including 60 Korean children and 28 North Korean refugee children with VDD. VDD was defined as a serum 25-hydroxycholecalciferol(25(OH)D)concentration <20ng/mL. Overweight was defined as a body mass index(BMI)>the 85th percentile(n=38), and normal weight as a BMI between 5th and 84th percentiles(n=50).All participants received vitamin D3 supplementation 2,000 IU/day for 8 weeks. The serum levels of 25hydroxycholecalciferol(25((OH)D, PTH, serum calcium, creatinine and urine calcium were measured before and after treatment.

Results: The mean age was 11.0+-1.6 years in normal -weight children and 10.9+-1.9 years in overweight children(p=0.83). After 8 weeks of treatment, 51.8% of normal-weight children and 49.6 % of overweight children of North Korean refugee children achieved Vitamin D sufficiency(p=0.24). 71.8% of normal-weight children and 69.6 % of overweight children of korean children achieved Vitamin D sufficiency(p=0.20). The mean serum 25(OH)D levels after vitamin D replacement were 31.2+9.6 ng/mL and 30.3 +-5.6 ng/mL in normal -weight and overweight children of North Korean refugees, respectively(p=0.20). The mean serum 25(OH)D

levels after vitamin D replacement were 38.2 ± 8.6 ng/mL and 33.3 ± 7.6 ng/mL in normal-weight and overweight of Korean children, respectively ($p=0.20$). The mean calcium/creatinine ratios after treatment were 0.09 ± 0.07 and 0.08 ± 0.06 in normal-weight and overweight groups in North Korean refugees children, and 0.08 ± 0.09 , 0.09 ± 0.07 in normal-weight and overweight groups in North Korean refugees children, respectively. No hypercalciuria was found in both group.

In multiple regression analysis, the response to vitamin D replacement was influenced by BMI ($b=2.0$, $p=0.04$, and sex ($b=3.0$, $p=0.02$) and national environmental influence ($b=1.0$, $p=0.04$).

Conclusion: Eight weeks of vitamin D replacement (2000 IU/day) is sufficient to overcome vitamin D deficiency in normal-weight and overweight children in both North Korean refugees and Korean children without any complications.

P3-35

Pseudohypoparathyroidism: Four cases reports

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Introduction: Pseudohypoparathyroidism (PHP) is a rare disease, characterized by parathyroid hormone (PTH) resistance and it refers to different mineral disorders of bone metabolism, classified as PHP type 1a (Albright-OHA Hereditary Osteodystrophy), PHP1b and PHP1c (OHA). Four cases reports: Four children were identified as having PHP, being three of them female. PHP was diagnosed at six years of age (three cases) and at seven years (one case). All children had diagnosis of hypothyroidism and one of them also had type 1 diabetes (T1DM) diagnosed at 12 years of age (six years after PHP diagnosis). One subject presented a mother with OHA phenotype, but normal laboratory assessment, characterizing pseudopseudohypoparathyroidism (PPHP). Different clinical manifestations were observed in the cases as craniofacial dysmorphisms (rounded facies, prominent forehead, flat nose...), brachydactyly, short neck, mild mental retardation, subcutaneous calcifications, short stature and obesity. Radiologic findings evidenced shortening of III, IV, and V metacarpals, epiphyses anomalies, lytic lesions and heterotopic ossification, suggestive of OHA. At diagnosis, all cases had elevated levels of PTH (Case 1: 807.3 pg/mL; 2: 281 pg/mL; 3: 111.5 pg/mL and 4: 132 pg/mL – reference value [RV] 15–65 pg/mL), hypocalcemia (1: 9.0 mg/dL, 2: 7.3 mg/dL, 3: 9.8 mg/dL and 4: 8.1 mg/dL) was observed in three cases (RV: 8.2–10.3 mg/dL) and hyperphosphatemia (1: 6.8 mg/dL, 2: 9.4 mg/dL, 3: 5.4 mg/dL and 4: 6.4 mg/dL) in only one case (RV: 4.0–7.0 mg/dL). All cases were treated with calcitriol with or without oral calcium supplementation and molecular analysis was yet not available. Discussion: PHP is characterized by renal defect in response to PTH, with hyperphosphatemia and elevated PTH, usually preceding hypocalcemia, being more commonly diagnosed during childhood. Genetically, PHP is caused by mutations in the gene that encodes the alpha subunit of G protein (GNAS), PTH

action signaling protein, thyroid stimulating hormone (TSH), gonadotrophins and adrenocorticotrophic hormone (ACTH) and others. The cases described in this series were all diagnosed in childhood and presented clinical and radiological manifestations suggestive of OHA.

P3-36

A Case of Robinow syndrome

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Introduction: Robinow syndrome is a rare autosomal recessive and autosomal dominant disorder affecting the whole skeletal system. Autosomal recessive robinow syndrome is characterized by shortness of the long bones and vertebra anomalies. Less than 200 cases of autosomal recessive robinow syndrome have been reported in the literature.

Case: The newborn was referred to pediatric endocrine clinic for disorder of penis development. He was born 3000 grams by cesarean section at 32nd gestational week. Family history revealed first degree cousin marriage. His physical examination showed his weight: 4000 grams (0.46 SDS), length: 47 cm (-1.62 SDS) and head circumference: 39 cm (1.58 SDS). On his physical examination, macrocephaly, broad forehead, low set ears, prominent and widely spaced eyes, short nose with upturned tip, broad and triangle-shaped mouth, overgrowth of gums, abnormal short fingers and toes were detected. His genital examination revealed micropenis, scrotalization occurred and the testes were in scrotum. Scrotal hyperpigmentation was not detected for adrenal diseases. Whole blood count, biochemistry analysis and thyroid function tests were normal. Serum FSH, LH and total testosterone levels were found to be compatible with minipuberte. Skeletal radiography showed fusion of hemivertebrae and ribs. Peripheral chromosome analysis revealed 46 XY. Homozygous IVS2-1G>C (c.176-1G>C) mutation was detected in the ROR2 gene in the long arm of the ninth chromosome by using the whole gene sequence analysis for Robinow syndrome.

Conclusion: Robinow syndrome should be considered in infants with mesomelic shortness, brachydactyly, craniofacial dysmorphic findings, gingival hypertrophy and undeveloped genitalia. Aarskog syndrome, I-cell disease, Omoyplasia and Jarcho-Levin syndrome should be considered in the differential diagnosis.

Abstract withdrawn

Mild Hypophosphatasia in a Family with a Novel Mutation in the *ALPL* gene

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Introduction: Hypophosphatasia (HPP) is a rare autosomal recessive or dominant genetic disorder characterized by the abnormal development of bones and teeth and deficiency of tissue non-specific alkaline phosphatase activity. These abnormalities occur due to defective mineralization, the process by which bones and teeth take up minerals such as calcium and phosphorus. The specific symptoms can vary greatly from one person to another, sometimes even among members of the same family.

Case: A 6 year old boy visited the clinic because of short stature, intermittent bone pain and mild developmental delay. He was born at 36 weeks via vaginal delivery, weighed 3.02 kg, and had hypoglycemia history after birth. The patient was the 1st child among 3 children of non-consanguineous parents with above average height. He was 105.6 cm (<3th percentile) in height, 17.4 kg (3rd percentile) in weight. He had high arched palate and large ears. Blood chemistry findings were as follows: total calcium 10.3 mg/dL (Reference range, RR, 8.3–10.0); phosphorous 5.3 mg/dL (RR, 2.5–4.5); alkaline phosphatase (ALP) 341 IU/L (RR, 104–338 in adult). Serum electrolytes, glucose, blood gases, hepatic and renal function tests, as well as routine urinalysis were normal. The growth hormone stimulation test showed normal response. Next-generation sequencing (NGS) was carried out, we identified heterozygous variant, including a truncating variant (p.Leu276Ter) in the *ALPL* gene. The mother of the patient were confirmed to have same variant with bone pain and relatively low ALP level. We could not find bone hypomineralization and flared metaphysis in skeletal X-ray, like former case reports of childhood type of hypophosphatasia.

Conclusion: We report a novel mutation of *ALPL* presenting with short stature and bone pain. We should consider mild hypophosphatasia in a patient with short stature and relatively low ALP level, and attempt to find genotype and phenotype correlation.

Uncommon association of Hypoparathyroidism and Rendu-Osler Syndrome

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Rendu-Osler-Weber syndrome (also called Hereditary Haemorrhagic Teleangiectasia) is an autosomal dominant disorder that results from multisystem vascular dysplasia. HHT syndrome has been described in association with autoimmune disorders, such as Hashimoto thyroiditis, lupus erythematosus, vitiligo, anti-phospholipidic syndrome and pernicious anaemia.

We present the case of a 6 year old girl with Rendu-Osler-Weber syndrome who was referred for endocrinological evaluation for moderate hypocalcemia discovered during a biochemical screening. The patient complained of paresthesia of the extremities without a history of carpal-pedal spasm, seizures or laryngospasm. Physical exam showed obesity (BMI 22.7 kg/m², above 97th percentile), no bone deformities, positive Chvostek sign, dental dystrophy. During the initial endocrinological evaluation, blood tests showed low serum calcium (8.1 mg/dl and 7.1 mg/dl in two different occasions), serum albumin (5.1 g/dl) and corrected calcemia (6.8 mg/dl), high phosphorus (7.4 ng/dl), low urine calcium (5 mg/500 ml, under the reserve of improper collection) and normal vitamin D levels (35.19 ng/ml). The parathyroid hormone concentration was inappropriately low (24.96 pg/ml). Cerebral CT scan showed no calcifications, hand X ray showed normal length of the metacarpal bones and no particular findings were found on electrocardiogram. Based on the clinical and biochemical evaluation the diagnosis of hypoparathyroidism was established. She was given alphacalcidol in doses of 0.25 ug and 500 UI colecalciferol, and put on a low phosphorus diet. She was advised to have an adequate intake of calcium. Under treatment, at one month evaluation the calcium corrected (serum calcium 8.4 mg/dl).

We present this case because of the rare association between HHT and hypoparathyroidism. To our knowledge, there is only one clinical case report of two brothers with clinical manifestations of HHT in addition to severe hypocalcemia associated to hypoparathyroidism. One possible explanation for this rare association can be the autoimmune etiology of hypoparathyroidism since other autoimmune disorders were reported to be found in HHT. However, the mechanism underlying the connection between HHT and autoimmune disorders is not yet clarified. Nowadays, there are no sufficient data to justify the coexistence of these two rare diseases.

P3-40

Barakat Syndrome (HDR Syndrome): Case Report

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Introduction: Barakat Syndrome (HDR Syndrome) is characterized by hypoparathyroidism (H), sensorineural deafness (D) and renal disease (R) caused by an autosomal dominant inheritance, being mostly associated to deletions in chromosome 10p14 or mutations in GATA3 gene. Case Report: A 9 years old male was admitted at an emergency complaining of upper and lower limbs pain and contractures that progressed with periodic tetany, lasting for four months years. At examination presented hypertension, muscle contraction of the upper and lower limbs, pain mobilization of both hands, feet and hip joints. Laboratory assessment demonstrated low total serum calcium (5.59mg/dL, reference value (RV): 8.2 to 10.3mg/dL), low parathyroid hormone (PTH) concentration (2.38pg/mL, RV: 15 to 65pg/mL), low serum phosphorus: 1.4 mg/dL (RV: 4-7 mg/dL), creatinine 1.17 mg/dL (Estimated Glomerular Filtration Rate-eGFR: 68 ml/min/1.73m² - RV: >90 ml/min/1.73m²), elevated calciuria (0.72 mg/mg, RV: <0.21 mg/mg) and albuminuria (41.8 mg/L, RV: <29 mg/L). The abdominal ultrasound evidenced diffuse increase in cortical echogenicity of the kidneys. The audiogram identified sensorineural hearing impairment. The clinical manifestations and laboratory findings of renal disease (tubulopathy), hypoparathyroidism and sensorineural hearing impairment strongly suggested Barakat Syndrome. Treatment was initiated with Teriparatide (20mcg/day, once a day), calcitriol and calcium carbonate supplementation, hydrochlorothiazide, Scholl's solution and elemental phosphorus. After three years of follow-up, the patients progressed with worsening of hearing impairment and renal function, bone mineral density reduction and nephrocalcinosis. Discussion: The HDR syndrome prevalence is unknown and is defined by different phenotypic expression (HDR, HD, DR, HR and D), being more frequently associated to sensorineural deafness (96.7%), hypoparathyroidism (93.3%) and renal disease (72.2%), all manifestations presented in our case. The molecular diagnosis (GATA3 testing) is important to confirm the syndrome in patients with isolated form of deafness or renal disease especially when there is another family member affected.

P3-41

Myelofibrosis in Severe Vitamin D Deficiency Rickets: A Case Report

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Background: Vitamin D deficiency is prevalent in infants and children in underdeveloped countries. Secondary myelofibrosis has been reported as a complication of severe rickets and in these children anemia, myeloid metaplasia and bone aplasia strongly suggested myelofibrosis.

Case Report: We report a case of myelofibrosis in two years old boy with severe vitamin D deficiency rickets and hepatosplenomegaly. He presented with grossly delayed gross milestones but his intellectual development was normal. The nutritional intake was very poor, comprising of breastfeeding and small quantities of home-cooked cereals. The child severely malnourished, with weight in -2.4 z score and length was -4.9 z score. he was anemic and had a wide open anterior fontanel and signs of florid clinical rickets. There were no neurological abnormalities except for mild generalized hypotonia. Radiological survey of the bony skeleton showed severe generalized osteopenia. extensive rickets of the thoracic cage and ends of long bones with splaying, cupping and fraying of metaphyses. No pathological features were noted. There was focal kyphosis in dorsolumbar region. Bone trephine clearly depicted replacement of hemopoiesis by fibroblasts with very occasional erythroid and myeloid precursors and no megakaryocytes were seen. Reticulin stain revealed significantly increased fibrosis, findings were consistent with myelofibrosis.

Conclusion: Rickets should be considered as one of the conditions that can lead to severe hematological disorders in infants.

P3-42

Congenital Hyperinsulinism in Kosova

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Congenital hyperinsulinism (CHI) is a rare inherited disease characterized by dysregulated insulin secretion from pancreatic β -cells leading to profound and recurrent hypoglycemia. The incidence of the disease in most countries worldwide is about 1 in 50000 newborns, and more frequent in countries with high consanguinity. Recurrent hypoglycemia can lead to neurological insult and permanent brain injury.

In Kosova in the last 15 years there were 4 cases diagnosed with CH, 3 cases in neonatal period and one case in infancy. The most frequently seen mutations were ABCC8 gene mutations. One of the patients required near-total surgical removal of the pancreas because of unresponsiveness in medical therapy.

In conclusion, clinical course and treatment response of patients with CHI are very heterogeneous. Long term and careful monitoring is needed. Awareness campaigns are needed to reduce brain damage in those patients.

P3-43**About a case of neonatal hypocalcemia**

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Background: Neonatal hypocalcemia is a common disorder, occurring more often in premature, low birth weight and asphyxiated infants, as in infants born to mothers with diabetes. Nevertheless its aetiology is heterogeneous ranging from iatrogenic, idiopathic and inherited metabolic abnormalities. Among these, Autosomal Dominant Hypocalcemia (ADH) is a rare syndrome characterized by the presence of inappropriately low concentration of circulating parathyroid hormone (PTH) with varying entity of hypocalcemia, high serum phosphate and relatively high urinary calcium excretion, due to an activating mutation in calcium-sensing receptor (CaSR).

Case Report: A female infant was born at 36 weeks of gestational age, IA 8-10, birth weight 2,560 Kg, from a pregnancy complicated by gestational diabetes treated with insulin. Laboratory examinations at birth showed hypoglycemia, hypocalcemia, high serum phosphate: proposita showed also cerebral calcifications at brain ultrasound. For the persistence of hypocalcemia and high serum phosphate, in association with very low levels of PTH, she was referred at 7 months of age to our Department for a suspected disorder of calcium metabolism. Her family history was positive for a maternal heterozygous mutation in CaSR which required oral supplementation with calcium and vitamin D; mother's dual X-ray absorptiometry was normal but calcaneus ultrasound showed poor bone quality. On admission, total calcium, ionized calcium (iCa), phosphate, were respectively 2.1 mmol/L (2.12-2.62), 0.95 mmol/L (1.07-1.32), 2.71 mmol/L (1.55-2.71); PTH was below the reference range (<3 ng/L; 12-72) while alkaline phosphatase and 25(OH) vitamin D were normal. An abdominal ultrasound showed hyper-echoic renal spots suggestive for mild nephrocalcinosis. Indeed, genetical analysis revealed a heterozygous single missense mutation S820F in exon 7 of the CASR gene (as her mother). Therefore, she started supplementation with calcium carbonate (320 mg a day) and vitamin D (400 UI). At 9 months of life, laboratory investigations revealed normal values of serum total calcium (2.12 mmol/L) and phosphate (2.58 mmol/L) despite ionized calcium (iCa) was persistent low (0.92 mmol/L) as well as PTH (8.96 ng/L).

Conclusion: ADH is a rare entity, however, it should be considered in the differential diagnosis of neonatal hypocalcemia. Moreover, diet plays an important role since at the moment of weaning the oral calcium intake decreased, possibly worsening hypocalcemia. Because of its rarity and its varying clinical presentation, a strict monitoring of the calcium balance is required together with a tailored adaptation of the dosing of supplementation to each single patient.

P3-44**Rare case report: asymptomatic hypercalcemia in children with lupus nephritis complicated with parathyroid adenoma**

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An 11-year-old boy came to our hospital on 2019-1-23 because of "discovered hypercalcemia for 4 months."

Past history: The child has a history of lupus nephritis for 2 years, and currently oral prednisone 12.5mg qd, mycophenolic acid 0.25g q12h, tacrolimus 1mg q12h for treatment. The lupus activity index was reviewed once a month due to lupus nephritis. At present, SLEDAI (lupus activity score) is 2 points, and the condition is well controlled.

Four months ago, serum calcium was found to increase by 2.83 mmol/L, without any complaint, vitamin D and calcium were discontinued. Serum calcium gradually increased in the past four months.

Physical Examination: No bone developmental deformity, no bone pain and tenderness, no abnormal findings in the physical examination.

Lab Testing: The serum calcium was 3.0 mmol/L, serum phosphorus was 1.16mmol/L, serum magnesium 0.64mmol/L, intact PTH 107.50pg/mL, ALP 224U/L, vitamin D 11ng/ml, 24-hour urine calcium 2.2mmol/L (0.046mmol/kg.d). Thyroid function and adrenal function are normal. Color Doppler ultrasound about thyroid, kidney, adrenal gland, testis, and pancreas were normal. There was no abnormality in the chest radiograph. Parathyroid gland color doppler ultrasound showed: hypoechoic nodules on the dorsal side of the left thyroid gland, considering hyperplastic parathyroid glands. ^{99m}Tc-MIBI parathyroid imaging showed: Parathyroid imaging (rear behind the left lobe) is positive.

Therefore, the clinical diagnosis is parathyroid adenoma, lupus nephritis. Unfortunately, there is no genetic testing result and no pathological findings of the parathyroid glands because parents do not agree with the test and surgery.

P3-45**Acute Lymphoblastic Leukemia; Atypically Presenting with Severe Hypercalcemia in a Palestinian Child**

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Severe hypercalcemia with total serum calcium concentrations above 15 mg/dL is a serious nonspecific life-threatening emerging disorder. Hypercalcemia usually results in nonspecific classic gastrointestinal and skeletal symptoms as anorexia, nausea,

weakness, polyuria, constipation and bone pain. It can be associated with metabolic, nutritional, inflammatory, genetic or malignant disorders, or can be drug-induced. Malignancy related hypercalcemia develops more aggressively and rapidly than hypercalcemia related to other conditions. Among hematological malignancies, hypercalcemia is common in lymphoma and multiple myeloma; however, it is rare in acute and chronic leukemias, especially in children. Hypercalcemia usually presents as a late complication in childhood leukemia. Here, we report a 10-year-old Palestinian female child who initially presented with severe hypercalcemia ($\text{Ca} 17.8 \text{ mg/dL}$) and low serum parathormone, and was diagnosed to have acute lymphoblastic leukemia in the absence of circulating blasts in the peripheral blood smear.

Key words: Hypercalcemia, hematological malignancy, Leukemia, circulating blasts

P3-46

Growth hormone treatment of a patient with X-linked hypophosphatemic rickets caused by PHEX mutation: effects on linear growth

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Background: Hypophosphatemic rickets (HR) stands for a heterogeneous group of rare disorders in which excessive renal phosphate wasting is observed. The main characteristics of X-linked HR (XLHR) (OMIM #307800) caused by mutation in *PHEX* (phosphate-regulating endopeptidase) gene (OMIM *300550) include bone deformities, disproportionately short stature, dental anomalies and hypophosphatemia with coexisting low renal phosphate reabsorption. The patient's growth may be improved by early treatment with vitamin D, phosphate, as well as recombinant human growth hormone (rhGH) which acts on growth cartilage directly, and increases renal phosphate reabsorption and serum phosphate levels. Recently, the new treatment option is burosumab, a monoclonal antibody which attaches to the FGF23 protein.

Objective: The aim of the study was to investigate the clinical phenotype and molecular background of HR in a patient in which XLHR was suspected as well as to analyze the effects of rhGH treatment on growth.

Patient and Methods: A girl aged 13 yrs and 2 months was diagnosed with HR at the age of 7 yrs and then treated with alfa-calcidol (42 ng/kg/d) and phosphorus (75 mg/kg/d). Because of severe bowing of lower limbs the girl underwent several orthopedic operations. Mother of the girl is also affected. Due to the diagnosis of growth hormone deficiency (max GH after stimulation was 7.4 ng/ml; $N > 10$) rhGH therapy was initiated at the age of 10.5 years (current dose of rhGH is 0.029 mg/kg/d). Molecular analysis was performed using total genomic DNA. *PHEX* gene was analyzed using standard PCR and direct sequencing method.

Results: The dominant clinical signs in a patient were bowing of legs, short stature and lumbar hyperlordosis. HtSDS at the time of diagnosis was -2.6. Current htSDS is -2.2 and the height gain during rhGH therapy was 0.4 +SD. Molecular analysis of *PHEX* gene revealed the presence of a known heterozygous mutation c.1645+1G>A in 5' splicing site of intron 15 (HGMD ID: CS992468) as well as a known polymorphism c.1769-10C>T (rs3752433) in intron 17.

Conclusions: Molecular analysis of *PHEX* gene is very important to confirm the clinical diagnosis of hypophosphatemic rickets, which is extremely important for early proper treatment to prevent severe bone deformities, improve final height as well as for appropriate genetic counseling in families with HR patients. rhGH therapy in patients with XHLR may be very effective in those with coexisting growth hormone deficiency.

Diabetes and Insulin

P3-47

Serum Catecholamines in children with type 1 diabetes mellitus

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Background: young children with type 1 diabetes mellitus (DM1) have a tendency to recurrent hypoglycemia. Increased sensitivity to insulin in young diabetes patients may be associated with features of secretion of catecholamine, particularly adrenaline.

The Aim: to explore the basal levels of catecholamine (epinephrine, norepinephrine, and dopamine) in serum of young children with type 1 diabetes mellitus to identify of possible relationships between autonomic neuropathy, declining levels of catecholamine and hyperinsulinism.

Methods: Basal levels of dopamine (DA), epinephrine (E), and norepinephrine (NE) in plasma were measured by the method of high performance liquid chromatography with electrochemical detection (equipment "Beckman's System Gold") in 31 children with type 1 diabetes (average age of 4.7 ± 0.26 years yrs; average duration of diabetes 2.1 ± 0.2 years). Body mass index (BMI) of children was averaged $15.4 \pm 0.8 \text{ kg/m}^2$. The degree of metabolic control was assessed by the levels of HbA1c, which were from 7.5% to 10.5% (average of $8.7 \pm 1.6\%$). Nobody of diabetes patients had clinical evidence of diabetic peripheral or autonomic neuropathy. All children receive insulin injections in average dose of $0.7 \pm 0.1 \text{ U/kg/day}$. The control group consisted of 8 healthy children (mean age 5.1 ± 0.2 years, average BMI $15.9 \pm 0.5 \text{ kg/m}^2$).

Results: norepinephrine, dopamine and total catecholamine were decreasing in young children with DM1 compared to the control group. Epinephrine in DM1 patients did not differ from the control. We compared of catecholamine in patients with good metabolic control ($\text{HbA1c} \leq 7.5\%, n = 16$) and the poor metabolic

control ($\text{HbA1c} > 8.0\%$; $n = 15$) and found that in children with a good control dopamine, norepinephrine, epinephrine and total catecholamine were below in comparison with healthy children. We analyzed the influence of the duration of the DM1 on levels of plasma catecholamine. Children with DM1 duration more than 2 years (2.9 ± 0.2 years, $n = 14$) had basal levels E, NE, DA and total catecholamine significantly lower compared with health control and patients with less diabetes duration (1.19 ± 0.22 years, $n = 17$), but statistical reliability when comparing these groups of patients had not been received. Not established correlation between the doses of insulin and serum catecholamine levels.

Conclusions: This study revealed the significant suppressing of total catecholamine, epinephrine, norepinephrine, and dopamine in young children with good metabolic control of type 1 diabetes mellitus.

P3-48

Oral Glucose Tolerance Test (OGTT) as a useful tool for early diagnosis of Type 2 Diabetes Mellitus and prediction of metabolic risks in children and adolescents

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Objective: Type 2 Diabetes Mellitus (T2DM) and obesity represent two major health hazards in children and adolescents, with rising prevalence. Several markers have been developed in order to diagnose T2DM and detect potential metabolic abnormalities. The objective of the study was to examine glucose tolerance in Greek children and adolescents and the differences in the glucose, insulin and c-peptide response curves between male and female children and adolescents during an OGTT. Also, to examine the association between the OGTT measurements and parameters, such as the gender, obesity, prediabetes, a family history of T2DM or hyperlipidaemia, and pubertal staging.

Subjects/Methods: A 3-hour OGTT was conducted in 89 obese or overweight children and adolescents and glucose, insulin and c-peptide concentrations were measured at seven time points.

Results: No significant differences were observed during the OGTT in mean glucose values between boys and girls. However, insulin and c-peptide concentrations were higher in the girls from $T=60\text{min}$ to $T=180\text{min}$. HOMA-IR was also higher in the girls, whereas IGI_{30} , a marker of beta-cell function, was lower. In patients with prediabetes, glucose concentrations were higher from $T=60\text{min}$ to $T=180\text{min}$ of the OGTT.

Conclusions: Our results show that overweight or obese girls may be at higher risk for future insulin resistance or beta-cell dysfunction. Also, not only the baseline and 2-hour measurements,

but also the $T=60$, 90 and 180 min measurements during the OGTT may be useful for diagnosing T2DM and predicting future metabolic risks in children and adolescents who are overweight or obese.

P3-49

Significance of the Early Marker of Nephrite Diabetic Nephropathy of the Uzbek Nationality with the First Type of Diabetes Mellitus

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Goal of Research: to assess the significance of the early marker of nephrite diabetic nephropathy of the Uzbek patients with the First Type of diabetes mellitus.

Materials and Methods: 100 patients with DM 1 were examined, including 80 patients with normoalbuminuria (NAU) and 20 patients at the microalbuminuria (MAU). The patients were from 1 to 14 years old with the disease duration from 1 to 5 years. They included 48 boys and 52 girls. 10 healthy children formed control group. Nephrite was identified by immunoenzyme method in the micro-flatbed format with the help of ELISA automatic device (USA). The normal range of nephrite in the blood serum are equal to $0.36 - 0.64 \text{ ng/ml}$.

Outputs and their Discussion: The patients under examination were split by two groups: 1st group with normoalbuminuria and 2nd one with microalbuminuria. The analysis of the clinical and anamnestic data demonstrated that 42.5% of examined patients had DM inherited burdening, at that, this indicator in the group with microalbuminuria accounted for 50%, and with normoalbuminuria - 35%. The diabetes duration in the 1st group was equal to 4.57 ± 0.50 , and in the 2nd one - 4.75 ± 0.60 years. The mean glomerular filtrate rate (GFR) was equal to 72.1 ml/min which corresponds to the second stage of the chronic kidney disease. According to the lipid metabolism, in particular, the triglycerids' level in the group with microalbuminuria was equal to 2.07 ± 0.41 , statistically valid exceeding the level in the first group - 0.89 ± 0.13 ($p < 0.05$). Nephrite level in the core group was equal to $0.65 \pm 0.06 \text{ ng/ml}$ statistically valid exceeding the level in control group, i.e., 0.45 ± 0.05 ($p < 0.05$). Obtained results demonstrate that nephrite identification at the normoalbuminuria stage is the early marker of the kidney damage.

Conclusions:

1. Clinical and anamnestic data demonstrated that DO manifestation rate does not always depend on DM duration.
2. The lipid metabolism indices, in particular, triglycerids' level aggravate together with progressing of manifestation of diabetic nephropathy.
4. Nephrite identification with 32.5% of the patients with 1st type DM at the NAU stage indicates the possibility of this protein application as DM early predictive marker.

P3-50**Hybrid diabetes with good response to metformin in an Adolescent with polyglandular polyendocrinopathy (APS2)**

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Introduction: Development of type 1 diabetes is well known in cases of type 2 autoimmune polyglandular syndrome (APS). We describe a case of APS2 who developed a hybrid form of diabetes that responded to metformin therapy.

Case: The patient is a 17.5 year old male patient who has been diagnosed with APS2 at the age of 13 years with primary adrenal insufficiency and autoimmune hypothyroidism .he has been on treatment with prednisolone 5 mg once daily, fludrocortisone 0.1mg once daily and levothyroxine 125 mcg daily .

At the age of 17 years, he was noticed to have excessive weight gain (BMI = 28.5 kg/m²) and acanthosis nigricans. He had no history of polyuria or polydipsia.

Investigation Showed: HbA1c = 7.2%, fasting RBS of 7 mmol/l and the 2 hour OGTT =14.6mmol/l, c-peptide of 2 ng/ml(0.9 to 7), fastinginsulin level was 40 pmol/l (20-570),HOMA-IR 1.8, auto-antibodies screen was positive for 3 antibodies (anti GAD65, anti-islet 2 ab and ant ZnT8 ab).

A continuous glucose monitoring (CGM) was done with IPRO for 7 days showed postprandial hyperglycemic episodes .

Due to the presence of signs of insulin resistance, high HbA1c, absence of hypo-insulinemia, and self-correcting hyperglycemia, we elected to start metformin 1000 mg BID and closely observe the glycemic control. One month later, the CGM showed marked improvement in the glycemic control with a drop in the HbA1c to 6.2%. The patient continued to be asymptomatic and his BMI decreased to 25.5kg/m², and he reported decrease in appetite .

1. Discussion:

Patients with APS-2 are characterized by at least two of the following three endocrinopathies: type 1 diabetes, autoimmune thyroid disease, and Addison's disease. The DR3-DQ2/DRB1*04:04-DQ8 genotype has been associated with type 1 diabetes in patients with APS 2. This is the first report that describes the occurrence of hybrid diabetes in a case of APS 2 that responded well to metformin therapy.

Conclusion: We reported a Hybrid form of diabetes that responded well to metformin therapy in an overweight adolescent with APS2

P3-51

Abstract withdrawn

P3-52**Off label use of CGM in a pediatric patient with type 1 Diabetes Mellitus under the age of 2**

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Introduction: Continuous Glucose Monitoring (CGM) is an asset for patients with type 1 DM. The Dexcom G6 is FDA approved for use in patients 24 months and older. This CGM does not require any calibrations or point of care interventions and lasts up to 10 days when inserted into the subcutaneous tissue. We present a case of a 17 month-old patient started on CGM (Dexcom G6), with subsequent improvement in glucose variability and continued excellent glycemic control (HgA1C <7.5%).

Case Presentation: Our patient was a 17-month-old male with type 1 Diabetes Mellitus, diagnosed at age 14 months. For 3 months he was managed with insulin injections and point of care glucose checks. His parents were struggling to check his blood sugar levels 4-8 times a day. His HgA1C was under control (less than 7.5 %), but parents were not happy with so many point of care interventions. Despite CGM not being FDA approved in children younger than 24 months of age, we decided to discuss off label use with the family in hopes of decreasing the number of blood sugar levels obtained via glucometer. All information regarding the Dexcom G6 was presented to parents (including risks/ benefits) and they were eager to move forward in order to avoid a point of care interventions. Informed consent was obtained prior to the transition to CGM. On follow up visits, parents were satisfied with the CGM and the fact that they do not have to struggle checking point of care glucose. Just as importantly they were able to avoid hypo or hyperglycemic events, prior to their occurrence. His HgA1C remained less than 7.5 %. The patient had no Emergency Room visits, no hospitalizations and a better quality of life for him and his family.

Conclusion: CGM Dexcom G6 is a very reliable device and its use can be beneficial for younger patients and their families. Our patient's data showed that he is more time in the range, with less hypoglycemic and hyperglycemic episodes. More importantly, quality of life and patient/family satisfaction was improved dramatically.

P3-53**A case of congenital hyperinsulinism due to ABCC8 mutation: A challenge to diagnosis, management, and treatment**

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Introduction: Congenital hyperinsulinism(CHI) is a rare complex disorder of hypoglycaemia attributable to inappropriate and dysregulated insulin secretion from the pancreas with an

incidence of 1:50 000(1:2500 in consanguineous populations). Genetics involves defects mainly in the KATP channel genes ABCC8 and KCNJ11.

Aim: We describe a male infant, presented with refractory hypoglycaemia the first week of life.

Subjects and Methods: The patient was admitted to the Paediatric Department with lethargy and reduced breastfeeding. He was the first child of healthy unrelated parents, born at term, birth weight 4.180gr; no history of perinatal asphyxia, no dysmorphic features. His mother had a normal oral glucose tolerance test(OGTT) during pregnancy. A low blood sugar(BG) 35mg/dl(1.9 mmol/l) on day one resolved with oral feeding. On admission, serum BG was 19 mg/dl(1.0 mmol/l), treated with intravenous(iv) dextrose. Consequently, he was started on iv Dextrose infusion and antibiotics, was monitored with hourly BGs(BMstixs) and had regularly 2-hourly feeds by mouth and nasogastric tube (NGT). A hypoglycaemia screen performed when BG was 23mg/dl(1.3 mmol/l); insulin and C-peptide levels were inappropriately high (10,6 μ U/l and 3,3 ng/ml respectively), blood and urine ketones were negative confirming the hyperinsulinemic hypoglycaemia. Septic screen was negative, cortisol, thyroid function tests, growth hormone levels, metabolic screen, carnitine and acylcarnitine were all normal. A central line was inserted to deliver concentrated dextrose infusion 12.5%(max 13.1mg glucose/kg/min), oral feeds were enriched with carbohydrate supplements; oral diazoxide and chloriazide were started, with progressively increasing doses of diazoxide (up to 15mg/kg/day) to maintain normoglycaemia (BG >60mg/dl(3.3 mmol/l). Gradually, the infant was released from iv fluids, central catheter and NGT were removed. He was discharged home on oral feeds with carbohydrate supplements with occasional hypoglycaemic episodes. Currently, he is outgrowing the doses of oral diazoxide and chlorothiazide while growth and development are appropriate for age.

Results: Genetic testing showed that the infant was compound heterozygous for two pathogenic ABCC8 variants, a diagnosis of autosomal recessive CHI, subtype ABCC8 (hyperinsulinism and diffuse disease).

Conclusions: CHI is a high-morbidity disease with lifelong consequences that require sustained medical input. It is important to optimize treatment to safeguard brain function and quality of life. Homozygous and compound heterozygous mutations are likely to suggest permanent forms of CHI. Recent experience suggests a reduction in the severity of hyperinsulinism over time. However, the management of CHI still remains a challenge.

P3-54

Relationship between Chloride infusion and Base Excess in initial treatment of pediatric diabetic ketoacidosis

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Background: In initial treatment of DKA, volume expansion should begin with 0.9% saline to restore the peripheral circulation. The use of large amounts of chloride-rich/bicarbonate-free fluids may cause the rapid development of hyperchloremic metabolic acidosis, which is described in ISPAD Clinical Practice Consensus Guidelines 2018.

The severity of DKA, defined by pH, HCO_3^- Base Excess (BE), is one of the factors in the prognosis. Advanced acidosis is a risk factor of cerebral edema, which is known to the major event in term of the life prognosis. We aimed to investigate the relationship between acidosis and Chloride infusion in our early treatment of pediatric DKA before administration of insulin.

Methods and Results: (Subjects) A total of 45 children with DKA admitted to seven institutions between 2010 and 2018 were retrospectively analyzed. Children in whom insulin or bicarbonate was administered before visiting our hospitals were excluded.

Methods: As an indicator of acidosis, BE was used to remove respiratory factors. We analyzed the average Chloride infusion rate (mEq/kg/h) and BE change rate (BE change/hour) from the start of infusion to before insulin administration. Anion gap and lactic acid were calculated and measured, respectively, as one of the factors of BE decrease.

We also divided the children into two groups according to average Chloride infusion rate, less than 10ml/kg/h (group S; N=21), and more (group R; N=24).

Results: The mean of BE change rate was -0.57 and its 95% confidence interval is -0.831 to -0.309, which was a negative value. There was no relationship among BE change rate and anion gap/lactic acid change rate. No significant difference in BE change rate between S group and R group were observed. The results were similar when analyzed separately for either moderate or severe cases.

Conclusions: The 95% confidence interval of the mean of BE rate of change in this study was in the negative range below zero, suggesting that the BE decreased in initial treatment of DKA with chloride-rich fluids.

P3-55**The role of patient adherence to insulin pump therapy with long-term treatment of type 1 diabetes**

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Background: Insulin pumps are widely used in the treatment of type 1 diabetes mellitus (T1D) in children because of numbers of advantages in compare with multiple daily insulin injections (MDI). However, the long-term efficacy of continuous subcutaneous insulin infusion therapy (CSII) in achieving and maintaining of diabet stability is still not resolved.

Purpose: Determine the effectiveness-related factors of glycemic control in a group of children and adolescents with T1D and CSII of 3 years and more.

Methods: We investigate the data of 239 children and adolescent from St.Petersburg with insulin pumps during 3 or more years. We analysed the dynamics of HbA1C level before and after pump therapy. HbA1C changes were evaluated depending on gender, patient age, baseline HbA1C level, as well as such factors as the frequency of using continuous subcutaneous glucose measurement (real-time CGM), temporary transitions from CSII to MDI by syringe pens, using a bolus wizard (BW).

Results: The obtained data of the last HbA1c value did not have reliable significant changes in comparison with the level of HbA1C before switching to the CSII (initial $7.82 \pm 1.46\%$, last $7.93 \pm 1.30\%$). The number of patients with HbA1C <7.5% was 42%. The best indicators were observed in the group of 4.5–7 years old, where the number of patients with HbA1c <7.5% was 67%; in the 12–18 group, only 35% of people had target HbA1C. In the majority of patients with baseline HbA1c <7.5%, its last value remained targeted, while in patients with HbA1c $\geq 7.5\%$, before switching to CSII only 23% reached the target level. Also, the best glycemic control in patients who used CSII constantly, in comparison with patients who periodically switched to MDI using a syringe pen ($p < 0.05$). HbA1C was lower in the group of adolescents 12–18 years old who used real-time CGM consistently, compared to the group that did not used of CGM ($p < 0.05$).

Conclusion: no statistically reliable significant change in the HbA1C level in children and adolescents on the CSII lasting 3 years or more compared with the initial value of HbA1C was detected. In the majority of patients with a target level of HbA1C (<7.5%) before switching to CSII, its last value remained within the target range, and in patients with an initial non-target level of HbA1c ($\geq 7.5\%$), only 23% reached target values that may be due to insufficient adherence to treatment and self-control methods.

P3-56**Long-term honeymoon period in Type 1 diabetes: True diagnosis MODY5; New mutation of HNF1B**

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Introduction: MODY is an autosomal dominant inherited type of diabetes that has been diagnosed before the age of 25 and caused by pancreatic β-cell dysfunction. HNF1B-MODY is more rare than other MODY causes and its frequency is between 1-5%. Mutations in HNF1B (MODY 5) are associated with pancreatic agenesis, kidney anomalies, genital system malformations and liver dysfunction.

Case: The patient is 8 years 2 months old girl whom fasting blood glucose level was 370 mg / dl, HbA1c: 13.9%, c-peptide: 0.29. Anti-GAD (+), anti-insulin(-), islet cell antibody (+). In the follow-up period 1 month after the diagnosis of honeymoon period, the patient entered the honeymoon period, which is claimed to be good for the use of a plant mixture of diabetes was learned. During the follow-up, insulin requirement was 0.16 / kg / day at 3 months and insulin was completely discontinued at follow-up. One year after the diagnosis, the baseline rate was found to be 78 mg / dl, c peptide was 0.83. Genetic analysis with suspicion of MODY was found to be heterozygous mutation c.C146G (rs770078634), a new mutation in the HNF 1B gene. In the abdominal ultrasonography of the patient, the pancreas was normal and the kidney had a double collector channel. Liver enzymes were normal.

Result: MODY is mostly seen in adolescence and young adulthood. However, it can be seen at earlier ages. Antibody positivity may initially lead to patients diagnosed with type 1 DM in rare cases. Although our patient was initially diagnosed with Type 1 DM, the need for insulin for a long time in the follow-up period brought MODY to mind. The patient family thought that the patient's diabetes had improved due to herbal remedy until the result of genetics. In patients with type 1 DM, the honeymoon period should be stimulating for MODY.

P3-57**Prevalence of Celiac disease (CD) and autoimmune thyroid dysfunction (AITD) in Indian children with Type 1 Diabetes**

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Objective: To estimate the prevalence of Celiac disease (CD) and autoimmune thyroid dysfunction (AITD) in children with Type 1 Diabetes.

Study Design: The analysis included 177 (83 girls, 94 boys) children and adolescents with a diagnosis of Type 1 Diabetes who were followed up for a duration of more than 2years at Sir Ganga Ram Hospital, a tertiary care hospital in Northern India.

Results: Biopsy-confirmed CD was present in 18 (10.16%) children. Duration of diabetes at the time of CD diagnosis was <2 years in 13 (72.22%), >2–5 years in 4 (21.05%), and >5 years in 2 (10.52%) children. Celiac disease was found in 11/94 (11.7%) boys and 8/83 (9.63%) girls.

We found 28 (15.81%) cases of autoimmune thyroid dysfunction, 27 (15.25%) cases of hypothyroidism and 1 of hyperthyroidism. Duration of diabetes at the time of diagnosis of AITD was <2 year in 17 (60.71%), >2-5years in 4 (14.28%), >5years in 3 (10.71%) children. AITD was present in 3 (10.71%) children prior to the diagnosis of Type 1 Diabetes. AITD was present in 18/83 (21.68%) girls and 10/94 (10.63%) boys.

Conclusion: CD and AITD are common comorbidities in children with Type 1 Diabetes. The findings support routine screening for CD & AITD in patients with Type 1 diabetes, particularly within the first 2 years after the diagnosis of diabetes. The prevalence estimate for CD is slightly higher in our study compared with a review conducted over three continents where an overall prevalence of 3.5% (1.9-7.7%) was reported. The difference in the prevalence could be because of the smaller number of children included in the study.

P3-58

Mauriac's Syndrome: a complication of poorly controlled type 1 diabetes mellitus in childhood and adolescence

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Background: Mauriac's syndrome (MS) may occur in patients with poor controlled type 1 diabetes mellitus (DM1), with often ketoacidosis, episodes of hyperglycemia and hypoglycemia, under the dose insulin. MS characterized growth retardation and puberty delay, Cushingoid obesity, moon facies, protuberant abdomen, hepatomegaly with transaminase elevation, dyslipidemia. Now it is a rare syndrome, firstly described by Mauriac in 1930.

Case Presentation: We report a case of 16-year-old girl with 12-years history of poor controlled type 1 diabetes mellitus and Mauriac's syndrome. The patient lived in a polar village, far from diabetology centers. She had few ketoacidosis and severe hypoglycemia episodes every year with treatment in hospitals. The patient was admitted in our diabetes clinic with hyperglycemia 360 mg per deciliter, and high level of HbA1c (14.2%), hepatomegaly, short stature and absence of secondary sex indications. On examination, the weight 45.2 kg, the height 136 cm (less than -2 SD) and the body-mass index 25.5. The skin was dry. Cushingoid obesity, moon facies, protuberant abdomen. The lungs were clear; the blood pressure was 160/100 mm Hg, the pulse 85 beats per minute. Ultrasonography of the abdomen revealed a fatty liver. Pubertal formula by Tanner: P1A1Ma1, amenorrhea. Her blood level of thyrotropin was 1.8 µU per milliliter, free T4 – 13.8 pmol per liter; LH 0.6 mU per liter; FSH 0.5 mU per liter. Somatotropin was elevated, but Insulin-like growth factor 1 (IGF-1, Somatomedin C) was decreased. Biochemical tests revealed high

total cholesterol – 6.5 mmol per liter, cholesterol LPH – 1.2 mmol per liter. Diabetes treatment: diet, insulin glargin and humalog in regime of multiple daily injections, 1.2 IU/kg, diabetes education. After 3 months HbA1c was 7.4%; glycaemia 8.0 – 180.0 mg per deciliter, the girl grew 6 cm and the liver sizes were normal.

Conclusions: Mauriac's syndrome is an uncommon condition resulting from poorly controlled DM1 in childhood and adolescence. Most clinical features of MS are reversible with improved glycemic control.

P3-59

Abstract withdrawn

P3-60

Clinical characteristics and literature review of special type of diabetes mellitus- thiamine-responsive megaloblastic anemia syndrome in infant with acute ischemic stroke

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Background: Thiamine-responsive megaloblastic anemia syndrome(TRMA) is a rare disease characterized by diabetes mellitus, megaloblastic anemia and sensorineural hearing loss. The disease can be accompanied by attack of stroke, which are rarely reported. To analyze the clinical characteristics of a case of thiamine-responsive megaloblastic anemia with attack of stroke in our hospital and review the related literature of this syndrome in order to improve the diagnosis and treatment of this disease.

Methods: Detect the organ system related to the syndrome. Blood sugar, hemoglobin, urine routine, blood routine, bone marrow puncture, Coombs test, brain magnetic resonance imaging(MRI), hearing, visual acuity and other examinations. After obtaining the informed consent, the SLC19A2 gene mutation loci of peripheral blood DNA were analyzed in the patient and his family.

Results: Children with intermittent cough, pale complexion and high sugar were treated for one month. Randomized intravenous blood sugar was more than 11.1 mmol/L and urinary routine showed ketone positive. Bone marrow reveals dysplastic hematopoiesis. Vitamin B₁₂/folic acid levels are normal and accompanied by sensorineural hearing loss. Leftsided hemiplegia and MRI revealed ischemic stroke in right Middle Cerebral Artery (MCA) region. TRMA syndrome was established for the patient and additional management included thiamine(100mg/d) was started. Biochemical analysis showed normal blood sugar without insulin injection and the hemoglobin concentration Hemoglobin could maintain normal. Leftsided hemiplegia was become better. After regular follow-up for 4 years, the blood sugar fluctuated between

5-9 mmol/L without insulin injection and the hemoglobin concentration Hemoglobin maintain normal. Leftsided hemiplegia improved significantly. However, sensorineural hearing loss has not improved. The result of SLC19A2 gene homozygous mutation c.726-727insA confirmed the diagnosis by amino acid frameshift mutation.

Conclusions: Pay attention to special types of diabetes mellitus when diabetes mellitus companied with other symptoms. Thiamine is the only drug used to treat TRMA. Different clinical manifestations have different reactions to thiamine. It is necessary to monitor blood routine, hearing, blood sugar, glycosylated hemoglobin and other indicators. Follow up for a long time to adjust drug dosage. TRMA is an autosomal recessive inheritance and genetic counseling is necessary.

p=0,002, p=0,015, p=0,02, p=0,007 and p=0,001, respectively). Serum P level was negatively correlated with pH and HCO₃ levels ($r=-0,495$; $p=0,000$ and $r=-0,383$; $p=0,003$, respectively) while it was positively correlated with serum BUN, Cr and C-FGF23 levels and TPR ratio ($r=0,634$; $p=0,000$, $r=0,487$; $p=0,000$, $r=0,230$; $p=0,047$, and $r=0,528$; $p=0,000$, respectively). Serum Mg level was negatively correlated with pH and HCO₃ levels ($r=-0,359$; $p=0,005$ and $r=-0,236$; $p=0,05$, respectively) while it was positively correlated with serum PTH level ($r=0,328$; $p=0,011$).

Conclusion: The results of our study suggest that the improvement in alkalosis and decrease in TPR ratio during DKA treatment are effective factors in the development of hypophosphatemia, whereas I-FGF23 and C-FGF23 do not have any role in the development of hypophosphatemia.

P3-61

The Effect of Fibroblast Growth Factor 23 on Serum Phosphorus Level in Children with Diabetic Ketoacidosis

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Aim: The pathophysiology of developing hypophosphatemia in children with diabetic ketoacidosis (DKA) has not been sufficiently elucidated. Fibroblast Growth Factor 23 (FGF23) is a hormone that causes phosphate excretion from the kidneys. The increase of FGF23 in children with DKA may explain the pathophysiology of hypophosphatemia in these children. The aim of our study was to investigate the effect of serum FGF23 on serum phosphorus level in children with DKA.

Materials and Methods: Our study included 30 patients with DKA. Data including age, gender, height and body weight measurements were recorded. Blood gase parameters including pH, PCO₂, and HCO₃ and serum BUN level were measured at the beginning of DKA treatment and at the lowest serum phosphorus level. Biochemical parameters including serum Cr, Ca, P, Mg, ALP, PTH, intact FGF23 (I-FGF23) and c-terminal FGF23 (C-FGF23) levels and tubular phosphate reabsorption (TPR) ratio were determined at the beginning of DKA treatment, at the lowest serum phosphorus level, and at the time of discharge.

Findings: The study was completed with 18 (%60) old and 12 (%40) new cases. The mean age of the patients was 140 ± 57 months. The mean serum Cr, Ca, P, Mg and ALP levels at the lowest serum phosphorus level compared to the onset of DKA treatment were significantly decreased ($p=0,000$, $p=0,002$, $p=0,000$, $p=0,000$ and $p=0,000$, respectively) while TFR ratio was significantly increased ($p=0,000$). The mean serum Cr level at the time of discharge compared to the lowest serum phosphorus level decreased significantly ($p=0,008$) while serum Ca, P, Mg, PTH, I-FGF23 and C-FGF23 levels and TFR ratio were significantly increased ($p=0,001$, $p=0,000$,

P3-62

What does the insulin pump change in children with type 1 diabetes? One-year clinical follow-up

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Aim: The insulin pump has an important contribution to quality of life and individualized insulin therapy. However, studies that observe clinical criteria can sometimes only reveal marginal benefits or minor differences. The use of insulin pump in our country has become recently widespread. Therefore, we aimed to share our clinical experience and to examine the effect of the pump on individual cases.

Method: The records of 167 patients who were treated with pump therapy in our child diabetes center were examined. Patients were included if diagnosed at least one year before the use of insulin pump, followed at least one year after pump insertion and anthropometric measurements as well as metabolic examinations are available at the control visits. HbA1C levels, lipid profiles, body mass index (BMI), microalbumin/creatinine ratio and total insulin requirement (IU/kg/day) were compared. Descriptive statistics of all the data in the study were calculated. Kolmogorov-Smirnov and Shapiro Wilk tests were used for normality assumption control of quantitative variables. While Paired Samples t test was used to compare the normal distribution variables measured at different visits, Wilcoxon test was used to compare the non-normally distributed variables.

Results: The mean age, diabetes and insulin infusion pump usage duration of 56 patients (27girls, 29 boys) were 12.8 ± 3.6 years, 6 ± 3 years and 2.5 ± 1.5 years, respectively. The HbA1c values were significantly lower at the individual visits and on average compared to the one-year average prior to the use of the insulin infusion pump ($p<0,001$). On the other hand, BMI values were significantly higher in individual visits and on average compared to the one-year average before the use of insulin infusion pump ($p<0,001$). There was no significant difference in LDL, triglyceride microalbumin/creatinine ratio before and after infusion pump. To look at the insulin requirements Carelink download system was used during the pump period. During the pre-pump period, only 30 patients could be compared because those with just carbohydrate/insulin ratio records were excluded. The mean insulin

dose was 0.73 ± 0.26 before the pump and 0.60 ± 0.27 during pump therapy. There was a nonsignificant decrease in insulin doses after the pump.

Conclusion: HbA1C levels regressed steadily after the use of insulin infusion pumps, however, BMI was found to increase steadily. Although the decrease in total insulin requirement is not statistically significant, regarding the higher BMI and lower HbA1C it may still significant from the clinical point of view.

P3-63

Severe heart disease can cause diabetes mellitus even in younger age: Case reports of two Japanese adolescent boys

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It is noted that patients with heart disease (HD) are likely to develop abnormal glucose metabolism and this metabolic deterioration usually occurs after middle age. However, we recently had two patients with congenital HD, who developed type 2 diabetes mellitus (DM) in their adolescence. The first patient underwent Fontan operation at 2 years of age for single ventricle and pulmonary atresia. His paternal grandfather had type 2 DM. He noticed polydipsia and polyuria at 15 years of age. His Body Mass Index (BMI) at that time was 13.87 kg/m^2 . Laboratory data revealed casual plasma glucose level of 562 mg/dL and HbA1c of 10.7%. After obtaining normal glucose levels by insulin therapy, a glucagon challenge test was performed and exhibited peak C peptide value of 3.58 ng/ml . His islet autoantibody was negative. He was diagnosed as type 2 DM and insulin therapy was stopped. He has been treated with Metformin 1500mg a day and keeps HbA1c as low as 6-percent levels. The second case had Blalock-Taussig shunt procedure for tricuspid atresia, ventricular septal defect, and pulmonary artery stenosis during infancy. His great-grandparents had type 2 DM. At a regular visit of 14 years of age, it was pointed out that his HbA1c level was as high as 7.6%. His BMI was 14.22 kg/m^2 . An oral glucose tolerance test and islet autoantibody test indicated type 2 DM. His HOMA-R and insulinogenic index were 0.97 and 0.48, respectively. Metformin was started and increased to 1000mg per day, followed by Sitagliptin Phosphate Hydrate 50mg daily. His glycemic control is rather insufficient and HbA1c stays around 7%. Neither patients could perform adequate physical exercise for their age because of chronic heart failure, but they did not have risky daily habits of DM such as excessive intake of carbohydrates. Actually, they had not been obese through their life. There are some reports indicating higher incidence of type 2 DM or metabolic syndrome in adults with HD. Cyanosis, heart failure and hypoxia are speculated as contributing factors as these phenomena. However, the mechanisms are not clearly understood. Our cases indicate that for patients with congenital HD and those with chronic heart failure their metabolic status should be checked even in adolescence and young adult age.

P3-64

De novo mutation of ABCC8 gene in a child with MODY developed at 25 months of age

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Introduction: Recently the incidence of type 2 diabetes was explosively increased in children and adolescents. The underlying mechanism of childhood-onset type 2 diabetes mellitus may be different to the adult-onset type 2 diabetes. Therefore, it is useful to conduct genetic study in children with type 2 feature to understand underlying cause of glycemic dysregulation as well as for the management of diabetes mellitus.

Case: A 25-month-old male was admitted at Urology department for the operation of scrotal mass and was referred to the department of Pediatrics because of hyperglycemia. Polydipsia and polyuria were reported from the parents. The child had no family history of diabetes mellitus. He was born at 36 weeks of gestation by normal vaginal delivery with birth weight of 2.61 kg . Initial HbA1c level was 13.6%. Serum glucose, insulin, and C-peptide were 413 mg/dL , 2.0 uIU/mL , and 0.45 ng/mL , respectively. Under the impression of type 1 diabetes, subcutaneous insulin injection was started with NPH and regular insulin with total insulin dose of 0.5 U/kg/day . We increased insulin dose up to 0.75 U/kg/day at discharge. After discharge, autoantibodies were reported as negative. Glutamic acid decarboxylase antibody was less than 0.2 U/mL (Normal range: $0\text{--}1 \text{ U/mL}$) and anti-insulin antibody was 5% (Normal range: $0\text{--}7\%$). He was hospitalized once again with uncontrolled blood glucose level, and discharged after increasing dosage of insulin up to 1 U/kg/day . During follow-up at outpatient clinic, his HbA1c was maintained well, ranging from 6.3 to 6.9%. We gradually reduced insulin dose to 0.58 U/kg/day , but intermittent mild hypoglycemia was noticed. Under the suspicion of type 2 diabetes, we changed treatment modality from NPH and RI to Lantus and Sulfonylurea (GlimepirideTM). Furthermore, we discontinued Lantus and added MetforminTM. Blood glucose level was well controlled without severe hypoglycemia or hyperglycemia. With a strong suspicion of MODY, we performed targeted exome sequencing which included 29 genes associated with monogenic diabetes. Mutation of p.Asp209Glu in the gene ABCC8 was found. Both parents did not have any mutation in the region of ABCC8 gene.

Conclusion: It may be recommended to perform the genetic test to find the candidate gene of type 2 diabetes mellitus which developed in children and adolescents. Here we report a case with de novo mutation of ABCC8 gene in a child with MODY developed at 25 months of age.

P3-65**Insulin-induced oedema in a child with newly diagnosed diabetes mellitus**

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Oedema is a rare complication of insulin therapy. It affects mainly patients with newly diagnosed type 1 diabetes mellitus, poorly controlled diabetes mellitus or patients on large doses of insulin. There are only a few case report showing that it is an uncommon and probably an under-reported complication. Two mechanisms are known: the sodium and water retention and vasoactive mediators release. The oedema tends to develop shortly after initiation of insulin therapy and resolves spontaneously within few weeks. Here we describe a case of insulin-induced oedema with newly diagnosed type 1 diabetes.

9 year old girl was admitted with polyuria, polydipsia, weight loss of 8 kg over 3 months. On physical examination, her height was 145,5 cm (1.62 SD), weight was 45 kg, (1.79 SD), body mass index was 21.4 (1.52 SD). Laboratory findings showed blood glucose level was 491 mg/dl, ketonuria with acidosis was present with venous blood pH of 7.2. Serum electrolytes and liver function tests were normal. Hba1c level was 13,5%. C peptide level was 0,3 ng/ml (1,1-4,4), anti GAD and islet cell antibody was positive. She was treated with insulin infusion at a rate of 0,1 unit/kg/hour and standard protocol for management of diabetic ketoacidosis was followed. On the 2nd day, insulin infusion was replaced with subcutaneous insulin (insulin aspart and glargin) reaching after a few days a dose of 2 unit/kg/day. She gradually developed pitting oedema of lower extremities and periorbitally on 7th day insulin treatment. Serum albumin level was normal. She had no proteinuria, liver failure or hyperaldosteronism. Other causes of oedema were excluded. The patients need for insulin was declined 1,3 unit/kg/day. Oedema spontaneously resolved within 3 days.

Insulin-induced oedema should be considered in the differential diagnosis in oedema in children and adolescents with type 1 diabetes mellitus. Loop diuretics is beneficial when spontaneous resolution does not occur. This case also supports suggestion in the literature of association between marked weight loss and large insulin doses.

P3-66**Familial hypercholesterolaemia as a cause of dyslipidemia in patient with type 1 diabetes**

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Introduction: Diabetes type 1 (DM1) in children can result in lipid disorders due to insulin deficiency. Familial hypercholesterolemia (FH) is a very common monogenic disorder with occurrence of 1:250 and it may lead to development of cardiovascular disease (CAD) in a very young age.

Case Report: Female patient with diabetes diagnosed at the age of 5, was referred to joint diabetes and lipid clinic due to high levels

of cholesterol. At the diagnosis of diabetes her total cholesterol (TC) level was 280 mg/dl, LDL cholesterol (LDL-C) of 201 mg/dl, normal HDL and triglycerides, her HbA1c was 9.5 % then. After 6 months in follow up in outpatient clinic her HbA1c was 7.5%, TC was 265 mg/dl and LDL-C was 191 mg/dl. Treatment with personal insulin pump was started at the age of 5.5 years to improve diabetes control. After 1 year from the diagnosis her diabetes metabolic control was good (HbA1c: 6.7 %) and lipids level again very high (TC 260mg/dl, LDL-C 190 mg/dl). As lipid profile did not improve patient was referred for genetic testing of *LDLR*, *APOB* and *PCSK9* genes. In patient's family history her grandfather from mother side had cardiovascular disease diagnosed at the age of 45 years. Patient's mother had not had lipid profile done in her life yet, so it was checked and TC and LDL-C was high as well. Patient was diagnosed with familial hypercholesterolemia due to mutation in *LDLR* gene inherited from mother. As familial hypercholesterolemia was confirmed and her cholesterol levels remained high, therapy with statin was implemented at the age of 7 years. After 6 month of treatment lipid profile became normal, patient did not report any adverse events. She is followed up in lipid clinic every year and all clinical and biochemical parameters are normal. Patient's mother was referred to Adult Cardiology Clinic.

Conclusions: Diabetes teams should remember that not only diabetes and poor metabolic control can result in lipid disorders in diabetic patients. It is important to diagnose and treat FH as early as possible to reduce risk of CAD especially in diabetic patients.

P3-67**What has changed in type 1 diabetes mellitus cases in the last eight years? A single center experience**

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Objectives: Type 1 diabetes mellitus (DM) is an autoimmune disease caused by the destruction of pancreatic beta cells. The frequency of Type 1 DM is increasing, and the highest incidence rate is in children under 5 years of age. It is estimated that children under the age of five will develop approximately 70% of the cases under the age of 15, with an increased incidence.

In our study, we aimed to evaluate the demographic, clinical and laboratory features of Type 1 DM patients diagnosed in our clinic during the last eight years.

Materials and Methods: The study included 323 Type 1 DM patients aged 1-18 years, diagnosed and followed in our pediatric endocrinology outpatient clinic at our Erciyes University School of Medicine. The anthropometric measurements, physical examination and laboratory findings of the patients at the time of the diagnosis were evaluated. The results were compared according to the gender, age and clinical presentation of the patients.

Results: 50.2% of the patients were female and 49.8% were male. The number of cases diagnosed under five years of age was 73 (22.6%) and the number of cases over 5 years of age were 250 (77.4%). In the 42.4% of the cases, there was a diabetes history in the family. According to the clinic at admission, 44.6% of the

patients presented with diabetic ketoacidosis. 44.2% of the patients presenting with ketoacidosis had severe ketoacidosis ($\text{pH} < 7.10$). 70% of children with severe diabetic ketoacidosis were under 5 years of age. Thyroid autoantibodies were positive in 10% and anti-endomysial antibody was positive in 8.5% of the patients. There were no significant difference in HbA1c levels between the patients without acidosis and patients with mild, moderate or severe ketoacidosis. C-peptide values were decreased in patients with ketoacidosis while acidosis worsening. When we grouped the patients according to the age at diagnosis, the mean age of the patients with severe acidosis under the age of five years was smaller ($p < 0.005$) while the average age of the patients with mild acidosis was smaller in patients over 5 years of age.

Conclusion: Similar to other autoimmune diseases, it is noteworthy that the diagnosis of diabetes has increased and the age of diagnosis has shifted to the earlier. In accordance with the literature, the frequency of diabetic ketoacidosis in our study was found to be higher as the age decreased.

P3-68

Seasonal variation and epidemiological parameters in children from Western Greece with Type 1 Diabetes Mellitus (T1DM)

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Introduction: A positive correlation between the onset of T1DM and winter has been suggested by studies conducted in different countries.

Objective: To investigate the seasonal variation of T1DM diagnosis and additional epidemiological parameters in children from Western Greece diagnosed with T1DM.

Methods: 105 patients, 44 males and 61 females, aged 1 to 16 years (mean: 8.2 ± 4 years) were studied. The date of the diagnosis, the order of birth, gestational age, birth weight, the mode of delivery, parental age and pubertal status were recorded from the patients' files.

Results: The mean age at diagnosis was 8.2 ± 4 years (min: 1, max: 16). The majority of the studied patients were diagnosed during the 6-month period of October to March (57 patients - 54%), as compared to the warmer months of April to September (48 patients - 46%). 51% of the children were first born and 87% were born at full term, whereas 11.5% were pre-term babies. 61% were born by vaginal delivery and 39% by caesarean section. The mean birth weight was 3261 ± 595 g (min: 1335g, max: 4550g). The majority of the patients were pre-pubertal at diagnosis.

Conclusions: Our results are in agreement with the reported seasonal variation of T1DM onset in other Greek, but also European, populations. The positive correlation between T1DM presentation and colder months may be explained by factors that

are related to lower temperature, such as infections. The majority of the children were first-born, born at full term, with a normal birth weight and pre-pubertal at diagnosis. Although most children were born by vaginal delivery, a significant percentage was born by caesarean section, which is a possible risk factor for the development of T1DM in susceptible subjects.

P3-69

An 8-year-old boy with Down syndrome who has had a history of transient hyperinsulinemia and was found to have type 1 diabetes during ALL treatment

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Case: An 8-year-old boy with Down syndrome. He was born at 36 week of gestation, birth weight was 1668 g (-2.5 SD). He complicated transient hyperinsulinemia (THI) treated with diazoxide for 2 months and hypothyroidism continuing treatment with levothyroxine. He was not detected transient abnormal myelopoiesis at neonatal period. He was diagnosed with precursor B-cell acute lymphoblastic leukemia (ALL) at age 8 years and started chemotherapy with a steroid, and blood sugar more than 200 mg/dl has become prolonged. Based on the combined drug use (steroids, L-Asparaginase) and serum C-peptide immunoreactivity 5.8 ng/ml (HOMA-R 6.9) in blood, we were diagnosed with drug-induced diabetes and started insulin treatment. After that, hyperglycemia appeared only when steroids and L-Asparaginase were administered, and insulin infusion were used intermittently. Eight months after the initiation of chemotherapy, prolonged hyperglycemia and low serum C-peptide immunoreactivity levels were observed even in the intermittent period of treatment, and an anti-gutamic acid decarboxylase (anti-GAD) positive was found (12.5 U/ml), and we diagnosed type 1 diabetes. HbA1c have been difficult to evaluate accurately due to the effects of anemia and blood transfusion associated with chemotherapy. The HLA type was DRB1*0405-DQB1*0401, a highest risk haplotype of type 1 diabetes.

Consideration: Because anti-GAD have not been evaluated before chemotherapy for ALL, it is unknown from when anti-GAD was presented. In this case, it is considered that the decrease in β -cell function is due to the combined influence of THI, glucose toxicity due to drug-induced hyperglycemia, and genetic background.

Conclusion: We experienced a case that presented with THI at birth was diagnosed with type 1 diabetes during ALL treatment at childhood. Even if it is considered secondary diabetes from the treatment history, autoantibodies should measure to distinguish type 1 diabetes.

P3-70**Indicators of Caries Risk in Children with Type 1****Diabetes Mellitus**

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Purpose: was to evaluate the interaction of caries risk indicators and metabolic control in children with type 1 diabetes mellitus.

Methods: The study included 50 children with type 1 DM and 50 healthy controls. Diabetic children were classified into 3 groups: well, fairly, and poorly controlled based on glycosylated hemoglobin level. Personal, family data, medical and dental history were collected. Children were examined for caries experience, plaque, and gingival condition. Saliva samples were obtained for culturing mutans streptococci, lactobacilli, and Candida, and colony forming units were counted.

Results: No significant differences existed between all groups regarding caries experience or mean log count of micro-organisms. Diabetic children differed significantly from healthy children in parental occupation and education, dental visits, oral hygiene, and plaque and gingival indices, whereas no differences were observed among children with different levels of metabolic control regarding these factors. Regression analysis identified mutans streptococci as a significant variable affecting caries experience in diabetic children.

Conclusions: Regarding the interaction of caries risk indicators and metabolic control on caries experience in diabetic children, the only variable that showed a significant effect was mutans streptococci

P3-71**Vitamin D status in Egyptian children with newly-diagnosed type 1 Diabetes and its relation to autoimmune destruction of pancreatic beta cells**

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Background: The relationship between 25 hydroxy cholecalciferol (25OHD) deficiency and autoimmune diseases including type I diabetes (T1D) is an ongoing area of research interest. Furthermore, vitamin D seems to affect β cells through calcium regulation, as insulin release is a calcium-dependent process. The aim of the study was to screen for (25OHD) deficiency in children with clinical onset of T1D and study the correlation between its serum levels and anti-glutamic acid decarboxylase antibody titre and serum C-peptide levels.

Methods: A cross-sectional study included 102 children with new-onset T1D. Serum levels of 25OHD, fasting and postprandial C-peptide and anti-GAD 65 antibody were assessed.

Results: This study included 52 females and 50 males with newly-diagnosed T1D, with a mean age of 8.8 ± 3.1 years. Serum 25OHD level ranged from 4.2 to 40.6 ng/mL with a mean of 15.5 ± 6.2 ng/mL. Among the studied patients, 74.5% were vi-

tamin D deficient and 23.5 were vitamin D insufficient. 25OHD status had significant negative correlation with anti-GAD 65 titre ($r = -0.31$, $p = 0.002$), while it correlated positively with serum levels of fasting C peptide ($r = 0.29$, $p = 0.002$) and postprandial C-peptide ($r = 0.27$, $p = 0.005$).

Conclusions: Vitamin D deficiency and insufficiency was highly prevalent in Egyptian children with new-onset T1DM. In agreement with the hypothesis that an inadequate vitamin D trigger autoimmunity, vitamin D level in the studied cohort was negatively correlated with anti-GAD antibody levels. Thus, it would be fundamental to study the effect of vitamin D supplementation in prediabetic state to slow the autoimmune cascade.

Keywords: type 1 diabetes; 25OHD; vitamin D supplementation; anti-GAD 65; C-peptide

P3-72**Hematologic indices indicating platelets activity in children with type 1 diabetes**

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Aim: The aim of this study was to evaluate hematological indices especially PLT indices in children with T1DM

Materials and Methods: In this case-control study which was conducted on 166 participants including 83 children with diabetes type 1 and 83 children hospitalized for thorough assessment of short stature, PLT count, MPV, PDW, WBC count, hemoglobin, blood sugar, PCT, P-LCR, and PLR were assessed. Patients with type 1 diabetes were divided into 2 groups including good and poor control based on HbA1c level below and above 7.5, respectively.

Results: Results showed positive correlation between age, hemoglobin, blood sugar, PCT, PLR, and HbA1c in children with diabetes. The area under the curve for PCT was 0.811 (0.663-0.959) and the cut-off point of PCT was 0.19. results indicated that only raised PCT (>0.19) was related with poor metabolic control and can put the patients to the risk of future cardiovascular events.

Conclusion: Multiple PLT parameters, and a scoring system for them in patients with type 1 diabetes mellitus can be recommended

The prevalence of hypertension and its relationship to glycemic control in children with type 1 diabetes mellitus

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Background: Type 1 diabetes (T1DM) is a chronic disease with many chronic complications as nephropathy, retinopathy and neuropathy or macrovascular complications as coronary artery disease and peripheral vascular disease due to the effects of hyperglycemia and dyslipidemia on vascular endothelial function. Moreover, in patients with T1DM, hypertension (HTN) is a significant contributor to the development of both micro- and macrovascular complications.

Aim: To determine the prevalence of HTN in children with T1DM attending Alexandria University Children Hospital (AUCH) and to study the relation between HTN, glycemic control and presence of other chronic complications such as nephropathy and retinopathy in these children with T1DM.

Method: Fifty children and adolescents with T1DM attending diabetes clinic in AUCH were subjected to history and full examination including blood pressure (BP) measuring and classification according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents to: Pre-hypertensive, Stage 1 HTN and Stage 2 HTN. HbA1c, microalbuminuria, lipid profile and ophthalmoscopy were done.

Result: Seven out of the 50 cases with T1DM (14%) had HTN. Most of the hypertensive cases were post pubertal (6 cases: 3 cases in Pre HTN stage, 2 in Stage 1 HTN and 1 in Stage 2 HTN). Significant positive correlation between BMI and systolic BP was found ($p<0.05$). HbA1c was significantly higher among the post-pubertal hypertensive group compared to pre-pubertal group ($p \leq 0.05$) with significant positive correlation between HbA1C and systolic BP in the whole group ($p=0.039$). Early nephropathy was detected in 85.7% of the hypertensive group ($p \leq 0.001$). The hypertensive diabetic children had a higher mean of lipid profile parameters ($p \leq 0.05$) with significant positive correlation between cholesterol level and systolic BP in the whole group as ($p = 0.002$). Only one case had diabetic retinopathy.

Conclusion: HTN is common among T1DM children and their blood pressure should be screened annually to guard against the development and progression of chronic complications.

Does metformin therapy prolong the honeymoon period in obese adolescent with hybrid diabetes?

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Introduction: Hybrid diabetes is a challenging form of diabetes that need to be more studied. We describe a case of hybrid diabetes with a prolonged honeymoon due to the use of metformin.

Case: Our patient is a 10 year old female patient who was diagnosed as type 2 DM on September 2017 at the age of 8 years. She was obese with $BMI = 29.8 \text{ Kg/m}^2$ with marked acanthosis nigricans. She had a patch of vitiligo on the face. Other systemic examination was unremarkable. Both grandparents had type 2 DM on oral treatment. The initial HbA1c was 8.7%. She was started on insulin basal and bolus with metformin along with behavioral and dietary modifications.

In few weeks, the insulin was stopped completely after a period of titration of the dose due to multiple episodes of hypoglycemia.

2 months later her BMI dropped to 24.5 kg/m^2 . On metformin 500 mg BID, her A1C dropped to 6.2%. Workup showed: fasting insulin level of 45 pmol/l, HOMA-IR was 1.4, positive autoantibodies were detected including anti islet cell antibodies, anti ZnT8 Ab and anti-GAD 65 antibodies. Thyroid profile and celiac screen were all normal. At this point she was counseled about the possibility of honey moon associated with type 1 diabetes and kept on flash continuous glucose monitor to observe her glycaemia. 8 months later; her A1C = 5.7%

One year after diagnosis, her A1C started to increase again (7.1%), her BMI was 22.5 kg/m^2 . Metformin was increased to 1500mg daily.

When followed again 15 months after diagnosis, the A1C was still increasing to 7.9%, c-peptide was 1.8 ng/ml, RBS 10 mmol/l. At this stage, she was started on a small dose of glargin insulin (0.12 unit/kg/day)

On subsequent follow up (17 months after diagnosis) she showed evidence of increased insulin demand to 0.2 unit/kg/day of basal insulin with HbA1c of 7.9% and her BMI = 20.5 kg/m^2 . Her mother attributed the worsening control to bad dietary habits. The diabetes etiology for her was challenged again especially after the subsequent visit that showed increasing A1C to 8.4%. At this point of her follow up, she was put back to basal bolus regimen.

Discussion & Conclusion: The role of metformin has been described as an adjunctive therapy in overweight young people with T1D. In this case it proved to be effective in hybrid diabetes with prolongation of the period without insulin therapy.

P3-75**A 16-year-old girl with prader-willi syndrome and type 2 diabetes mellitus**

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Background: Prader-Willi syndrome (PWS) is a complex genetic disorder with implications on the endocrine and neurologic systems, metabolism, and behavior. Early in life, PWS is characterized by hypotonia and failure to thrive, followed by obesity and hyperphagia. Patients with PWS develop hypothalamic dysfunction which may lead growth hormone deficiency, hypogonadism, hypothyroidism, adrenal insufficiency and poor bone mineral density. Traditionally, obesity is a hallmark feature of PWS which may be complicated by metabolic syndrome and type 2 diabetes mellitus (T2DM). T2DM is very common in 25% of PWS adults, although rarely develops during the childhood years.

Case Presentation: a 16-year-old girl with Prader-Willi syndrome, morbid obesity, hyperlipidemia, hypertension, fatty liver, type 2 diabetes mellitus, hypogonadism, severe mental retardation, deficit speech. Medical history: approximately 3.5 years before diabetes mellitus type 2 was diagnosed (polyuria and polydipsia); metformin was administered. Glycated hemoglobin (HbA1c) levels were 7.4% or lower. The patient was admitted in the diabetes clinic with hyperglycemia 382 mg per deciliter (21.2 mmol per liter), and high level of HbA1c (10.6%), insulin glargine was added. On examination, the weight 102.8 kg, the height 150 cm (- 2SD) and the body-mass index (BMI) 45.7. The skin was dry, scratching, hyperemia and maceration in the perineum. The lungs were clear; the blood pressure was 150/100 mm Hg, the pulse 115 beats per minute. Ultrasonography of the abdomen revealed a moderately fatty liver and hepatomegaly. Pubertal formula by Tanner: P₁A₁Ma₁, amenorrhea. Gynecologist found complete vaginal atresia. Her blood level of thyrotropin was 2.1 µU per milliliter, free T₄ - 15.7 pmol per liter; LH 0.6 mU per liter; FSH 0.5 mU per liter; C-peptide 2.3 nmol per liter. Biochemical tests revealed high total cholesterol - 8.0 mmol per liter, cholesterol LPH - 1.09 mmol per liter. Diabetes treatment: diet, metformin 2000 mg, glargine 30 IU per day. After 3 months HbA1c was 7.6%; and glycaemia 72.0 - 160.0 mg per deciliter.

Conclusions: This study shown the need for screening of type 2 diabetes mellitus in children with Prader-Willi syndrome.

P3-76**Extra attention to be paid when looking after boys with Type 1 Diabetes Mellitus in Oman**

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Introduction: More than 1,106,500 worldwide children were living with type1 diabetes mellitus (T1DM) in 2017¹. Researchers concluded that better glycaemic control is associating with lesser complications of this chronic condition. Target HbA1c is recommended to be <48mmol/mol(<6.5%) and <53mmol/mol(<7%) as per NICE and ISPAD respectively². The glycaemic control represented by HbA1c was worse amongst the British girls³, similar to boys in recent Saudi study⁴, our neighbouring country, but it was unexpectedly poorer in Omani boys compared to girls.

Aim: To examine the HbA1c in our cohort of patients and to identify the role of gender factor on glycaemic control.

Methods: Retrospective 1 year (2018 only) observational study was carried out. Data were captured from the electronic medical records of children and young people up to the age of 17 years under the care of paediatric endocrinologists at Sultan Qaboos University Hospital.

Results: 162 patients (F=89) with T1DM. Age at diagnosis ranged from 1.1 to 13.9 years, median of 6.9 years. Majority of them 145(89.5%) were on multiple daily injections regimen (MDI).

Higher HbA1c values were witnessed in teenagers. However, there was no correlation between mean HbA1c and duration of diabetes.

Interestingly, the median HbA1c amongst teenager boys was much higher than of females, 76 mmol/mol (9.2%) compared to 69mmol/mol (8.5%).

We have learnt that boys, especially in bigger Omani families, are getting somehow early independence in looking after themselves which leading to less supervision from parents resulting in poorer glycaemic control.

Conclusion: It is important to take the cultural factor in consideration when looking after children and young people with T1DM. Extra attention and support to be provided for the growing young males. We would recommend examining this observation in other Arab countries who share the same traditions with Omanis.

P3-77**Factors affecting the preservation of C-Peptide Secretion in Egyptian children with Type 1 Diabetes**

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Background: Type I diabetes is associated with progressive destruction of pancreatic β-cells with gradual decline of insulin secretion. C-peptide is considered the best indicator of endogenous insulin secretion in patients with diabetes.

Aim of the Work: Evaluate the effect of different variables associated with preserved pancreatic beta cell function at one year after diagnosis of children with type I DM.

Patients and Methods: The study is cohort study comprising 93 newly diagnosed type I diabetic children (46 females and 47 males) with age ranging from 3.25 to 16 years. They were divided into 2 groups: preserved pancreatic functions (stimulated c-peptide [S-CP] \geq 0.6ng/ml), non-preserved pancreatic function (S-CP $<$ 0.6ng/ml). Mixed meal stimulated C-peptide and glycated hemoglobin was assessed at time of diagnosis and after 12 months of follow up during regular visits at outpatient clinic. The variables assessed were age at diagnosis, gender, residence, Z-score of weight, height, body mass index (BMI), family history of type I DM, season at diagnosis, presence of DKA at diagnosis, glycated hemoglobin (HbA1c), insulin regimen and total daily insulin dose.

Results: Preserved pancreatic function was associated significantly with older age ($P = 0.04$), colder months (winter and autumn) ($P = 0.03$) and higher glycated hemoglobin levels at diagnosis ($P = 0.04$). Residence, gender, body weight, height, BMI, presence of DKA at diagnosis, total insulin dose and insulin regimen failed to predict preserved C-peptide levels at 12 months follow up.

Conclusion: Older age, colder seasons and initially higher glycated hemoglobin at diagnosis remains significantly associated with preserved C-peptide after 12 months follow up.

P3-78

Prevalence of Fatty Liver in Children with Type 1 Diabetes Mellitus Attending Diabetes Clinic of Alexandria University Children's Hospital

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Background: The non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide. It is not uncommon in children with type 1 Diabetes Mellitus. It is often asymptomatic and discovered accidentally.

Aim: The aim of this work was to screen the presence of fatty liver among children with type 1 DM attending the diabetes Clinic of Alexandria University Children's Hospital and its relation to the state of glycemic control and lipid profile.

Methods: The study was conducted on 40 children diagnosed with type 1 diabetes aged from 5 years to 18 years with a duration of diabetes for more than 3 years. All children were subjected to the following: History taking, full detailed physical examination, anthropometric measurements. Liver enzymes (ALT&AST), lipid profile, and HbA1C were done. Transabdominal ultrasonography was done for detection of fatty infiltration of the liver.

Results: The mean duration of diabetes was 7 ± 2.9 years. Ten out of 40 children with diabetes (25 %) had fatty liver as evidenced by U/S. Hypercholesterolemia was found in (5%) of the children. All patients had normal triglycerides, HDL and LDL. (62.9%) of patients had poor glycemic control, but the relation between the degree of glycemic control and development of fatty liver shows no significant difference.

Conclusion: Type 1 diabetes-related fatty liver is not uncommon and its screening is needed.

P3-79

Hyperinsulinemia as a consistent feature in the extremely rare donohue syndrome

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Donohue syndrome (also known as leprechaunism) is an extremely rare and severe autosomal recessive genetic disorder. Leprechaunism derives its name from the fact that people with the disease often have elfin features and are smaller than usual. Leprechaunism is also characterized by abnormalities of the endocrine system ; such abnormalities include hyperinsulinemia. Due to the mutation in Insulin receptor gene, infants with leprechaunism fail to use insulin effectively (insulin resistant). Because of this, they may experience postprandial hyperglycemia and abnormally hypoglycemia when not eating. Additional abnormalities resulting from improper function of the endocrine system include abnormal enlargement of the breast and clitoris in females and the penis in males. In some cases, cysts have formed in the ovaries. Hypertrophic cardiomyopathy may be seen in these patients as in diabetic mother babies. Here we are representing the first reported Egyptian case with this extremely rare disorder . A 5 months old boy born to consanguineous parents with history of dead female infant with the same condition . The patient was presenting with stunted growth, large penis, protuberant nipples, prominent and low-set ears, flaring nostrils, very thick lips and gingival hyperplasia . Hyperinsulinemia due to Insulin resistant was full blown in our patient.

Provisional Diagnosis of leprechaunism was reached thorough clinical evaluation, a detailed patient history, identification of characteristic symptoms and physical findings. The diagnosis required measurement of insulin levels, with a blood test, and confirmation of defective insulin binding on the cells known as fibroblasts.

Molecular testing of the Insulin receptor gene mutation in the index case and parents is recommended for confirmation of our diagnosis . This will aid in providing proper genetic counseling for the family and prenatal diagnosis in upcoming pregnancies.

P3-80

A Real-Life Experience with A New Insulin Co-Formulation Degludec/Aspart For One Year In Poorly Controlled Children And Adolescents With Type 1 Diabetes

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Achieving optimal metabolic control can be extremely challenging in some children and adolescents with T1DM. The adherence to multiple injections/day is among the leading causes

of suboptimal control. Recently insulin degludec/aspart co-formulation (70%IDeg+30%IAsp: IDegAsp) has become available. Because of the longer-duration of IDeg, and retained individual pharmacokinetics of IDeg and IAAsp, we wanted to test insulin IDegAsp's efficacy in our patients with poor glycemic control.

Objective: We investigated the number of hypoglycemic episodes, diabetic ketoacidosis (DKA) frequency, and HbA1c levels before and after changing to IDegAsp.

Methods: Patients >4 years of age who had diabetes duration of >1 year and on poor control on basal-bolus insulin regimens (≥ 4 injections/day) were included in the study. IDegAsp treatment were offered to the patients with HbA1c of $>8.5\%$, or having DKA while on insulin treatment or labile diabetes and/or omitting insulin injections. Their insulin regimen were changed to one IDeg/Asp injection and two IAAsp injections (three injections/day) with dose titration.

Results: Forty-six patients (20 girls) were included in the study. The mean age and the age of onset of diabetes were 12.9 ± 3.4 (4-18) and 5.2 ± 3.1 years (1.0-13.7), respectively. The reasons for the transition to IDeg/Asp were requirement of two doses of basal insulin (5 injections/day) (18), frequent episodes of hypoglycemia (9), daily glucose variability (9), frequent DKA (6). Ten patients discontinued IDeg/Asp due to continuing hyperglycemias (n:5), dosing difficulties (n:3), transition to pump (n:1) or DKA (n:1).

36 patients were evaluated at the 1st year of IDeg/Asp treatment. Their metabolic control parameters were compared to that of the previous year. No change in HbA1c levels has been detected after switching to IDegAsp (p:0.96). However, the number of self-reported mild-moderate hypoglycemia decreased significantly (p<0.05). There was only one episode of severe hypoglycemia before and after the regimen change. In previous year before regimen change, 8 DKA attacks in 7 patients were detected, which decreased to 3 DKA attacks in 3 patients during the year on IDegAsp (p:0.15). No significant change in BMI-SDS (p:0.13, but the decrease in insulin doses (unit/kg) (P<0.05) were detected.

Conclusion: IDegAsp regimen could be useful in patients with frequent hypoglycemia and DKA attacks, who have poor compliance with multiple injections. Better adherence to treatment because of less injection number and longer duration of IDeg could preventive for DKA in some cases.

P3-81

Cerebellum malacia lesions as a result of severe diabetic ketoacidosis in 12 month old patient

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Introduction: Diabetic ketoacidosis (DKA) in children is related with high risk of severe complications in the central nervous system such as cerebral oedema, hematoma and thrombosis. The occurrence of cerebral oedema in children with DKA is around 1: 100 and is higher in young children with severe acidosis and in whom DKA is the first manifestation of the disease.

Case Report: 12-month-old patient diagnosed with diabetes was admitted to the Paediatric Diabetes Department after

hospitalization in the Paediatric Intensive Care Unit due to coma caused by severe diabetes ketoacidosis. Before admission to hospital baby's parents noticed failure to thrive, polyuria and polydipsia, 2 days before admission antibiotic treatment of pharyngitis was prescribed. On the day of admission, patient's parents noticed that child had abnormal breathing and did not respond normally, therefore they went to hospital. In laboratory tests severe metabolic acidosis and hyperglycemia were found and intravenous therapy with fluids and insulin was started. After 15 hours of treatment patient had an episode of bradycardia which was resolved after administration of mannitol. After 2 days child was discharged from PICU and transferred to the Diabetes Department.

At the admission to Diabetes Department patient was conscious and stable, but not very active. Due to severe acidosis and long-lasting disturbances of consciousness, brain MRI was performed, and areas of increased signal in PD, T2 dependent images were detected in the cerebellum and both cerebellar hemispheres, which did not strengthen after contrast and showed diffusion limitations, which could be a result of acute ischemic and hypoxic changes. In the following days, the child's condition improved, he was more active and according to parents he was behaving as before DKA. Stable glucose levels were achieved by treatment with personal insulin pump. Physiotherapy was advised and his psychomotor development in the second and third year of life was going well. One year after DKA, brain MR was performed again, in which there were malacia lesions in the cerebellar hemispheres seen, the rest of brain structures were without any visible changes. Patient remains under diabetic and neurological care. Diabetes control is good and there are no concerns about his development.

Conclusions: In young children with type 1 diabetes fast diagnosis of diabetes is crucial as the first manifestation of the disease may be severe metabolic acidosis with high risk of complications. Children with severe acidosis require intensive treatment of DKA due to possible complications.

P3-82

Assessment of testicular volume by Ultrasound in Children and Adolescents with Type 1 diabetes

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Introduction: Poorly controlled type 1 diabetes affects the hypothalamic pituitary axis and is likely to have a negative impact on spermatogenesis and result in infertility. Further, a chronic complication of diabetes may also be angiopathy of testicular vessels. Thus, at our center for children with diabetes, testicular ultrasound evaluation is performed on adolescent boys with duration of diabetes > 2 years.

Objective: To perform the ultrasound examination of the testis in boys with poorly controlled diabetes with disease duration of > 2 years.

Methodology: Adolescent boys with T1D with disease duration of > 2 years attending diabetes out patient clinic for

underprivileged children in a tertiary level care pediatric endocrine unit in Pune, India, were included in the study. Demography, age, disease duration, anthropometry, treatment history and associated illnesses were recorded. HbA1c was assessed and complications were screened. Complications screening included testing for retinopathy, neuropathy and nephropathy. USG scrotum was performed to assess testicular volume and additional findings were noted. Data analysis was performed using SPSS 25.

Results: A total of 94 boys were studied with a mean age of 14.5 ± 3.8 years, mean disease duration was 5.8 ± 2.1 years; mean height and BMI Z scores were -0.75 ± 1.1 and -0.71 ± 1.3 respectively. The mean right testicular volume and Z score were 6.3 ± 4.7 cc and -0.9 ± 0.9 respectively. The mean left testicular volume and Z score were 6.3 ± 4.8 cc and 0.3 ± 0.5 respectively. Mean HbA1c was $10.7 \pm 1.9\%$ at the time of study. Last 5 years average HbA1c was $10.7 \pm 1.9\%$. Microlithiasis was observed in 11 patients (11.7%) and 17 (18%) had a prominent mediastinum. There was difference in HbA1c and complications those who had microlithiasis vs those who did not had.

Conclusion: Testicular volume though small was within the reference range among poorly controlled patients with T1D. Testicular Microlithiasis was noted in 11% patients. Given the higher incidence of testicular tumors and impaired fertility, performing testicular USG is important.

with poor response to a 6 months course of low-dose testosterone stimulation at age 15 years. Wolfram syndrome was suspected after he presented with neurological signs including progressive sensorimotor axonal polyneuropathy, dizziness, and nocturia and polyuria with voiding difficulties associated with an increased bladder capacity at the age of 16 years. Laboratory investigations and thirst test revealed the diagnosis of a diabetes insipidus centralis. Desmopressin supplementation was started successfully decreasing urine output and improving voiding difficulties. Renal function, hepatic function, thyroid function, audiologic examination and magnetic resonance imaging of the brain were normal. Furthermore, no optic atrophy or diabetic retinopathy were observed. Genetic testing of the *wolframin* gene is pending. Interestingly, repeat antibody testing for type 1 DM revealed positivity for anti-insulin-antibodies.

Conclusions: This case report highlights the need of careful clinical vigilance for atypical features in children having (non-autoimmune) DM. Not only typical monogenic forms should be considered, but also mitochondrial causes such as Wolfram syndrome, which require specific genetic workup and have important consequences on clinical monitoring and outcome. Furthermore, the diagnosis of Wolfram syndrome may have therapeutic implications for such patients as with DM associated with endoplasmic reticulum stress-mediated β -cell loss, GLP-1 receptor agonists may improve metabolic control.

P3-83

Diabetes mellitus in a 16-year-old boy developing multiple neuro-endocrine dysfunctions in the course: Is it type 1 diabetes or Wolfram syndrome, or both?

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Introduction: Autosomal recessive mutations in the Wolfram syndrome type 1 gene are responsible for the classical Wolfram syndrome (*OMIM_ 222300*), also known by the acronym "DID-MOAD" (diabetes insipidus, diabetes mellitus (DM), optic atrophy and deafness). The gene encodes wolframin, a membrane glycoprotein, which helps to regulate the calcium homeostasis in the endoplasmic reticulum of many different tissues, including the pancreatic β -cells and the neuroendocrine cells. Typically, Wolfram syndrome is characterized by early-onset, non-autoimmune DM, usually without significant ketoacidosis at first presentation. The associated symptoms, like optic atrophy, diabetes insipidus, sensorineuronal deafness, urinary tract abnormalities, neurologic degeneration and endocrine dysfunction manifest with inconstant severity and prevalence as well as variable age of onset, often delaying the precise diagnosis.

Objectives: We report the case of a 16-year-old boy who presented with insulin-dependent DM without ketoacidosis at the age of 5 years and developed multiple neuro-endocrine dysfunctions over the following decade.

Results: Since diagnosis, the DM was difficult to control (hemoglobin A1c levels between 8.1-9.7%) despite high-doses of insulin were used (1.7 IU/kg/day). Family history was positive for type 2 DM. During follow-up, the patient showed severe, progressive reduction of visual acuity, short stature and delayed puberty,

P3-84

A low-carbohydrate diet improves metabolic control in a type 1 diabetic child without side effects

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Background and Aims: Despite intensive insulin treatment of type 1 diabetes (T1DM), metabolic control remains suboptimal, especially in children. In an attempt to optimize postprandial glycaemia, some families decrease the amount of carbohydrates contained in a meal. While "low-carbohydrate diets" may improve metabolic control in some selected populations, controversies remain around the risk of hypoglycemia and ketoacidosis and the impact of such diets on growth and development of children.

Case Report: We report the case of a child whose whole family started a low-carbohydrate diet when it was seven years old, in an attempt to induce weight reduction for the parents. The child adhered to this diet and subsequently developed T1DM at the age of eight years. It continued the same diet after diagnosis.

Glycated hemoglobin (HbA1c) was 13.8% (127.3 mmol/mol) at the time of T1DM diagnosis and decreased to 7.3% (56.3 mmol/mol) three months later. During subsequent follow-up, it ranged between 5.9% (41 mmol/mol) and 6.4% (46.6 mmol/mol). The diet of the child consisted of 10 – 30 g carbohydrates per day and numerous supplements such as omega-3 fatty acids, vitamins A,

B1, B2, B6, C, D, E and K, as well as folic acid and niacin were taken on a daily basis. Almost every meal or snack the child ate was homemade by the mother of the family, including numerous "low-carbohydrate" desserts and bread, made of almonds, linseed and Chia seeds. Hypoglycemic events were rare and the insulin needs ranged from 0.11 to 0.24U/kg/day. Despite these very low insulin needs, ketone measurements were normal. After two years of carbohydrate restriction, weight gain and linear growth remained normal and no episode of ketoacidosis was observed. Lipid and cholesterol levels also remained within normal limits.

Conclusions: According to the International Society for Paediatric and Adolescent Diabetes (ISPAD), it is recommended that 50 – 55% of energy be derived from carbohydrates for children with T1DM. Potential adverse outcomes such as abnormal growth, increased risk of hypoglycemia, increased risk of ketoacidosis, dyslipidemia, vitamin deficiencies and psychological side effects may arise due to carbohydrate restriction. While there is currently no evidence to support this approach in children with T1DM, it is essential to accompany families who choose carbohydrate restriction in order to keep in touch with them on a long term and thus to be able to carefully monitor side effect of their dietary regimen.

P3-85

To Find Prevalence of Type 1 with Autoimmune Thyroid Disorders, Age, Duration,Thyroid Antibodies, Growth and Glycemic variability in Indian Scenario

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Objective: To Find Prevalence of Type 1 with Autoimmune Thyroid Disorders, Age, Duration,Thyroid Antibodies, Growth and Glycemic variability in Indian Scenario.

Methods and Plan: This is retrospective observational Multi-centric Study carried out in our four (4) centers of DIA CARE, Ahmedabad during January to December 2018, We divided Diabetes Type 1 Patient with Autoimmune Thyroid disorder According to Age, Diabetes Duration,Growth and Glycemic Variability in Indian Scenario.

We studied consecutive 100 patients of Type 1 Diabetes with Thyroid Disorder during January 2018 -December 2018. We recorded data regarding Age, Growth, Diabetes Duration and Diabetes Glycemic variability.

Results: We studied total 100 (Diabetes type 1 with Autoimmune thyroid disorder) at 4 centers of Dia Care, Ahmedabad, Gujarat, India.

Data Recorded between Age – 15 + 5

<u>Children with Diabetes Type 1</u>	<u>100</u>
<u>Male</u>	65
<u>Female</u>	35
1-3 Age	12
6-10 Age	18
10-18 Age	48
More than 18	22

Data Recorded Type 1 patient Duration of Diabetes

<u>Duration Of diabetes</u>	<u>Children with type 1</u>
0-2	46
3-6	32
7-12	22

Data Recorded in variation in Thyroid Antibodies.

<u>Thyroid Antibodies normal Range</u>	<u>Thyroid Antibodies in Abnormal Range</u>	<u>Variation in thyroid Antibody.</u>
28	31	41

Data Recorded according to Growth

(Every Six months clinically examined, including thyroid gland palpitation, blood pressure and assessment of puberty status and growth)

<u>Normal Growth according to Age</u>	<u>Delayed Growth according to Age</u>
41	59

Data Recorded in patient with glycemic variability.

(Glycemic variability according to Daily Glucose measurement and HbA1c according to time interval.)

<u>Good/Stable Glycemic control</u>	<u>Glycemic variability</u>	<u>Poor Glycemic control</u>
22	48	30

Conclusions: Study Indicate high Prevalence between Age Group 10 to 18 years.

Relationship between Thyroid Disorder and Diabetes mellitus type 1 is characterized by a complex interaction, thyroid autoimmunity being more prevalent in people with type 1

Higher percentage among study of Type 1 children with thyroid disorder are male and duration of diabetes detected 0 – 2 years.

Higher Percentage of Type 1 children with thyroid disorder have Variability in Thyroid Antibodies.

Higher Percentage of Type 1 Children with thyroid disorder have delayed Growth.

Higher Percentage of Type 1 children with Thyroid disorder have Glycemic variability.

Diabetes type 1 children with thyroid disorder found high percentage in Variability in thyroid antibodies, Delayed Growth and High Glycemic Variability in Indian Scenario.

P3-86

Clinical profile of paediatric patients with type 1 diabetes mellitus at a tertiary health care center in the oriental region of northeastern Morocco

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Introduction: The growing pandemic of type 1 diabetes is considered as an enormous multifactorial public health challenge

in the world. Many targeted interventions should be provided to improve type 1 diabetes management especially during childhood and adolescence.

The purpose of this study is to elucidate the epidemiological, clinical and management profile of type 1 diabetes in Moroccan children and adolescents

followed up in the endocrinology department of Oujda's Mohammed VI university hospital.

Material and Methods: This is a retrospective data analysis of children and adolescents with type 1 diabetes followed up in the endocrinology department of Oujda's Mohammed VI university hospital.

Results: 83 children and adolescents with type 1 diabetes were involved in the study. The number of patients diagnosed with type 1 diabetes was higher during the cooler months of the year compared to the warmer ones, and a positive family history in first-degree relatives was reported in 23% of patients.

The overall mean age at diagnosis was 12,8 years and the most commonly reported presenting symptoms were polyuria (85%), polydipsia (82%), and weight loss (63%)

Diabetic ketoacidosis at initial presentation was diagnosed in 40% of patients and 34% of cases were admitted for unstable glycaemic control ; with an average of initial hemoglobin A1c value of 12,3 %.

The classic b-cell autoimmune markers were surveyed in 57% of cases ; and 67% were found positive for antiglutamic acid decarboxylase antibodies (GADA).

All the included patients were screened for co-occurring autoimmune disorders ; and hypothyroidism was detected in 13% and coeliac disease in 9,1% of cases.

Chronic degenerative complications were noticed in 15% of patients with retinopathy in 10,4% and diabetic kidney disease in 7,2%.

Basal Bolus insulin regimen was adopted in 95,7% and 48,3% of patients were enrolled in flexible insulin therapy training programmes. Insulin pumps were used in 14% of cases.

Conclusion: Endocrinology department of Oujda's Mohammed VI university hospital offers a personalized healthcare, for each child or adolescent with type 1 diabetes in order to improve metabolic control, decrease the risk of hypoglycemia and enhance the quality of life

P3-87

Comprehensive Analysis of HLA System Class II DRB1 in children with Insulin Dependent Diabetes Mellitus in the North Azerbaijan and Iranian Azerbaijan

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Key words: Human Leukocyte Antigen system, DRB1 alleles

Diabetes mellitus is one of the diseases, the genetics of which has been most widely studied. In 40-50 % cases it is connected

with Human Leukocyte Antigen system. The major genetic determinants of this disease are DQ and DR genes "DR3" and "DR4" haplotypes create high risk for diabetes.

Insulin dependent diabetes mellitus risk is very high among the Iranian Azerbaijanis possessing HLA DR3-DQ2 haplotypes. In this ethnic group DRB1*0301 (82/5% with 11.3%), DQA1* 0501 (82.5% with 6.3%), DQB1*0201 (81.3% with 35%) alleles represent higher risk compared with healthy people. In Iranian Azerbaijani nationality the frequency of DRB1*0401 is significantly higher (76.74% in comparison with 23.26%).

Aim. The research aimed to study the relationship between diabetes mellitus and HLA genes in two azerbaijan populations. In the populations the alleles of HLA polymorphic genes are observed in different versions.

Materials and Methods: HLA-DRB1 gene has been determined in children in North Azerbaijan (106 sick, 209 healthy). Saliva has been used in control groups and blood analysis in diabetic patients. The results have been calculated with Conexio ATF Assign™ and SCORE™ computer program. The statistic calculation have been analyzed using Pearson's Chi-squared and odds ratio has been computed. The genetic examination have been carried out in the Children's Hospital of Oakland Research Institute, in California, USA.

Results and their Discussion: Both European and Asian alleles exist in North Azerbaijan population. DRB1*03:01, DRB1*04:02, DRB1*04:05, DRB1*09:01 alleles contribute a high risk for diabetes, but DRB1*15:01 (Europe) and DRB1*15:02 (Asia), DRB1*11:01 alleles are protective in nature.

Conclusions: DRB1 alleles vary widely in the studied populations. DR3 and DR4 haplotypes are associated with diabetes mellitus and they are found in broad intervals. Some alleles (such as, DRB1*11:01) possess contradictory features in different populations. The complete study of DRB1, DRB3, DRB4, DRB5, DQA1, DQB1, DPA1, DPB1, A, B, C genes will provide possibility to enlarge upon the haplotypes.

P3-88

A case of Type 2 diabetic adolescent with sleep apnea who was successfully stopped metformin after adenotonsillectomy

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Sleep deficit is the well known risk factor for obesity in children and adult. Adenotonsillar hypertrophy is the main cause of obstructive sleep apnea(OSA) in childhood. Adult type (type II) OSA is increasing in obese children. Eleven year old boy visited our clinic with chief complain of polyuria, polydipsia onset two weeks ago. His grandmother and father are type 2 diabetes mellitus. Adenotonsillectomy was recommended for tonsillar hyperthropy (Grade 3) and had snoring for 3 years. Also He has asthma, allergic rhinitis. In his physical examination; His body weigh, height and his BMI were 79.0kg (+ 3.3SD), 152.0cm(+ 0.9SD) and 34.19kg/m² (+ 4.0SD). His Blood pressure was 100/60 mmHg. His tonsil

was enlarged of bilateral grade I and Mallampati score was 1. He showed acanthosis nigricans at his armpits and neck. Laboratory test showed as follows; Random blood glucose : 260 mg/dL, HbA1c 9.3 %, AST/ALT: 112 / 288 IU/L, HOMA-IR: 18.3, C-peptide(FBS): 2.2 ng/mL, Islet Cell Antibody, Anti GAD Ab and Insulin Ab were all negative. On admission, Insulin and metformin therapy started after evaluation for diabetes mellitus. Snoring and excessive daytime sleepiness were noticed. Polysomnography was done despite small tonsillar size. Moderate severe OSA was found with apnea-hypopnea index : 9.0/hr. Adenotonsillectomy was done at 11th HD. Tonsil size was enlarged (4.5x2.3x2cm, 4x2.5x2cm) at operative field. Insulin was stopped and metformin started at 7th POD. And finally metformin was stopped at 60th POD.

We are reporting a case with obesity and type 2 diabetes improved blood glucose control and fatty liver after adenotonsillectomy. It is necessary to screen the presence of sleep apnea in children and adolescents with obesity or diabetes, especially with family history of diabetes.

P3-89

A mitophagic response to iron overload-induced oxidative damage associated with the PINK1/Parkin pathway in pancreatic beta cells

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An increased iron overload led to a disorder in glucose metabolism. However, the mechanism through which iron overload induces beta cell death remains unknown. The present study revealed that ferric ammonium citrate treatment inhibited cell viability *in vitro*, induced a decline in mitochondrial membrane potential, increased oxidative stress and activated mitophagy. These effects could be alleviated by a reactive oxygen species scavenger. In summary, we demonstrated that increased iron overload induced cytotoxicity in INS-1 cells primarily by activating oxidative stress and further triggering mitophagy in the PTEN-induced putative kinase 1/Parkin pathway. These findings may shed some light on the mechanism of iron toxicity-mediated pancreatic beta-cell dysfunction.

P3-90

A management challenge of Acute viral hepatitis A in a child presented with DKA as a first presentation

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Background: Diabetic patients frequently develop a constellation of electrolyte disorders. These patients are often potassium-, magnesium- and phosphate-depleted, especially in the context of

diabetic ketoacidosis. Patients with type-1 diabetes are predisposed to develop a spectrum of liver diseases, which includes fatty liver, steatohepatitis and cirrhosis. The association of hepatitis A infection with type-1 diabetes is extremely rare.

Case Report: A nine year old female child diagnosed with diabetic ketoacidosis as the first presentation of diabetes mellitus (she was complaining of polyuria before presentation and nocturnal enuresis) she was admitted to PICU to receive the appropriate treatment. We noticed that her electrolytes were disturbed; hypomagnesemia, hypocalcemia, hypokalemia and hyponatremia and hypophosphatemia. So urine spots were collected and high urine levels of these electrolytes were found confirming that the girl had a tubular defect. Also serum creatinine were elevated, serum complement 3 sample withdrawn and it was normal. During her stay at the hospital, she developed icterus therefore we investigate to discover the cause of her jaundice. Hepatitis B, C, CMV, EBV, HIV were negative while HAV IgM were positive. Her random blood sugars during the maintenance phase were low despite being on low requirements to her age so, thyroid and celiac profile were withdrawn and pending.

Conclusion: Elevated liver enzymes in diabetic patients may be due to causes other than fatty liver and autoimmune hepatitis as infectious hepatitis

P3-91

Association of type 1 diabetes and celiac disease in child

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Introduction: The association between type 1 diabetes (T1D) and celiac disease (CD) has been described by many authors in both children and adults. The link between these two pathologies was identified more than 30 years ago, especially by pediatricians. The aim of this work was to study the clinical, biological, and evolutionary features of CD in diabetic children compared to a control group of non-celiac diabetic children.

Patients and Methods: Retrospective study of a cohort of 20 T1D children with CD compared to a control group of 20 non-celiac diabetic children collected in the Pediatric Department of Tahar Sfar University Hospital of Mahdia over 30 years.

Results: The prevalence of CD in children with diabetes was 2.7%. Diabetes was revealed in celiac children by ketoacidosis in 70% of cases versus 40% in controls. The mean duration of diabetes progression was 8.8 ± 1.8 years in celiac patients versus 10.2 ± 2.1 years in controls. The mean age of discovery of CD was 7.2 ± 3.1 years, 3.4 years in mean after the discovery of diabetes with a sex ratio of 1.5. At the time of diagnosis of CD, 50% of children were asymptomatic, 40% had growth delay, 14% had abdominal pain, 16% recurrent hypoglycaemia, 7% chronic diarrhea, 62% anemia, and 75% CD positive antibodies. Jejunal biopsies showed total villous atrophy in 40% of cases, subtotal villous atrophy in 30% of cases and partial villous atrophy in 30% of cases. Gastric biopsy revealed associated Helicobacter pylori gastritis in 50% of cases.

After initiating a gluten-free diet, 64% of celiac children had poor diet adherence because of their low socioeconomic status. Short stature was observed in 52% of celiac patients versus 15% of controls. Hypoglycemia was a cause of re-hospitalization twice as common in celiac children than in the control group. Mean HbA1C in celiac patients was 10.6% versus 9.1% in controls.

Conclusion: Our study echoes those in the literature by emphasizing the high prevalence of CD among children with diabetes that is higher than that seen in the general population. The high prevalence of DT1-CD in our series justifies routine screening for CD in diabetic children. This may improve the balance of diabetes in children with CD, especially those with digestive symptoms or stunting, and avoid the complications of CD.

P3-92

Case of family neonatal diabetes with KCNJ11 gene mutation: dynamics monitoring

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Background: The most common cause of permanent neonatal diabetes (PNDM) is heterozygous activating mutations in the *KCNJ11* gene encoding the pore-forming Kir6.2 subunit of the pancreatic beta cell KATP channel.

Objective and hypotheses: To determine the dynamic of carbohydrate metabolism in family transferred from insulin to sulphonylureas (SU).

Method: We studied a family (mother and child) with PNDM diagnosed within the first 6 months of life. Carbohydrate metabolism was studied HbA1c, C-peptide during 8 months and 5 years of SU therapy. The *KCNJ11* gene was sequenced by Sanger.

Results: the mutation in *KCNJ11*, R201H was identified in the child and the mother at the age of 2 months and 28 years. Insulin has been canceled. At the beginning of treatment, the child's daily dose of SU was divided into 6 doses (0.27 mg / kg / day) with each feeding, but at the age of 10 months, the frequency of taking the drug was 4 doses / day (0.17 mg / kg / day). After 8 months of SU treatment, an improvement in glycemic control was observed (HbA1c level decreased 5.15% versus 13.9%). The level of C-peptide increased from 0.09 ng / ml to 0.5 ng / ml after 8 months of treatment of SU. Daily monitoring of glycemia showed a noticeable decrease in fluctuations in glycemia and improved glycemic control (from 13.8 [2.6-26.6] mmol / l before treatment with SU to 6.0 [3.3-10.2] mmol / l - after). After 5 years of monitoring, the child grew and developed according to age, taking SU twice a day (1 mg / s -0.05 mg / kg/day). HbA1c level - 5.9%, C-peptide 0.41 ng / ml. The average rates of glycemic fluctuations per day were (4.8 [8.6-3.8] mmol / l

Conclusion: With the manifestation of diabetes mellitus during the first 6 months of life, the patient after genetic testing shows the pathogenetic treatment of SU. The daily dose of SU in a child over the course of 5 years of observation decreased on average by 40% from the initial dose due to the stabilization of carbohydrate metabolism. However, a decrease in the level of C-peptide by 20% from the initial one was also noted. Further observation required.

P3-93

Severe and inaugural diabetic ketoacidosis in children: Experience of a pediatric Tunisian Department

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Introduction: Ketoacidosis is often indicative of diabetes in children in our Tunisian context. It can be severe and life-threatening, with mortality in the order of 1 to 2%.

Methods: We report the results of a retrospective study over a period of 2 years (from 1/01/2017 to 31/12/2018) on all cases of inaugural ketoacidosis of type 1 diabetes mellitus in children, collected at the pediatric department of Mohamed Tlatli hospital in Tunisia.

Findings: During this period, 10 cases of ketoacidosis decompensation were identified. The average age was 6.16 years, with male sex predominating (sex ratio= 4). The ketoacidosis decompensation was inaugural in all cases.

Four of the admitted diabetic children had presented a severe ketoacidosis decompensation.

The clinical features were dominated by polyuropolydipsic syndrome present in 9 cases two weeks to one month before decompensation, dehydration was almost constant with collapse found in 2 cases, polypnea translating acidosis observed in 6 cases, the state of consciousness was altered in 3 cases.

Biologically: mean blood sugar was 24.39 mmol / l, mean alkaline reserve was 6.64 and renal function was disrupted in 7 cases.

All patients were perfused for an average duration of 23.3 hours with extremes ranging from 15 hours to 41 hours.

The evolution was favorable in all cases.

Conclusion: Severe diabetic ketoacidosis remains frequent and life-threatening for young patients, while the diagnosis of early childhood diabetes is easy, immediate and inexpensive. The challenge is to reduce the frequency of ketoacidosis as a revealing circumstance of diabetes in children, by bringing the diagnosis to an earlier stage of the disease.

P3-94

Role of renal scintigraphy as an early predictor of chronic renal damage in children and adolescents with type1 diabetes

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Background: Chronic kidney disease (CKD) was defined by structural or functional renal abnormalities, or an estimated glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m². A child with CKD may develop many complications such as: anemia, poor growth and nutrition, bone and mineral disorders,

cardiovascular complications, and complications of hemodialysis, and peritoneal dialysis.

Aim: Assessment of severity of renal impairment and staging of chronic kidney disease in type 1 diabetic children and adolescents using serum creatinine, renal ultrasound and renal scan.

Patients and Methods: This analytic cross sectional study was conducted on 41 children and adolescents having type 1 diabetes mellitus, aged 5 to 18 years old with duration of diabetes more than 5 years, presented at Pediatrics department, Suez Canal University Hospital, Ismailia, Egypt. Full medical history, thorough clinical examination, laboratory investigations including H A1c, serum creatinine, renal ultrasound and renal scanning were performed for assessment of chronic kidney damage.

Results: The mean age of patients was 13.9 ± 3.03 years; 63.4% were males & 36.6% were females. The mean GFR of the studied group using radionuclear Scintigraphy was (66.1 ± 12.08) ml/min / 1.73m^2 ; 14.6% of them were in stage I CKD with GFR more than 90 ml/min / 1.73m^2 and 85.4% were stage II CKD. By using renal ultrasound, all of the studied population had normal renal ultrasound findings. Eighty three percent of the whole group were clinically asymptomatic. In this study, none of the studied group had elevated serum creatinine.

Conclusion: Renal Scintigraphy can be used as an accurate measure for assessment of GFR for early detection of renal dysfunction and chronic morbidity in type 1 diabetes mellitus in children and adolescents and can be used as an early predictor of chronic kidney disease better than using renal ultrasound or serum creatinine.

P3-95

Changes in the Microbiome of Pre-Type 1 Diabetic Children

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Introduction: Type 1 Diabetes (T1D) is an autoimmune disease where β -cells of the pancreatic islets are destroyed. The vast majority of T1D cases are not due to genetic predisposition, implying that the prevalence is associated with environmental, nongenetic factors. One such factor is the microbiome and its correlation with T1D has been investigated in a multitude of studies.

Aims: To investigate whether the current literature is providing evidence that there is a link between onset of T1D and the microbiome.

Methods and materials: Search for primary literature was done using PubMed Central. Changes in the gut microbial communities

Two of the main factors identified that have the capacity to change the microbial diversity are age and cessation of breastfeeding. Breastfeeding is selective for lactose degrading bacteria, while incorporation of fibre is aided by transketolase. Because of this, the fluctuations in the microbial communities during this transitional period is evident.

A positive correlation associated with predisposed T1D child was found between *Blautia*, *Ruminococcus*, *Rikenellaceae* and *Streptococcus* genera outgrowth even prior to disease onset. Some species within these genera are described as pathobionts,

potentially causing inflammation. Significant correlation was found between increase of *Bacteroides* and anti-islet antibodies.

Gut integrity was also compromised in pre-T1D cases, as butyrate producing bacteria were low. Butyrate is especially important as it maintains the gut epithelial stability and ensures bacterial localisation. Additionally, there was an observation of increased production of triglycerides and branched-chain amino acids from *Blautia* and *Ruminococcus*.

Discussion: Cessation of breastfeeding and age are linked, as reduction in breastmilk and incorporation of solid foods on the basis on age of the child, which in turn induces the changes in the microbiome. The presence of *Blautia*, *Ruminococcus*, *Rikenellaceae* and *Streptococcus* in pre-T1D children cannot only cause gut inflammation but also induce permeability of the gut, which can be aided by the reduced number of butyrate, during which microorganisms can reside in the intraperitoneal space, causing increase in inflammation. Moreover, the increase of triglycerides pre- and post-T1D onset increases the unpredictability of hypoglycaemia. The positive correlation between *Bacteroides* and anti-islet antibodies advances the further destruction of β -cells and aiding disease onset.

Conclusion: It is evident that the gut microbiome has an effect on T1D onset and progression, with these findings highlight the importance of understanding the microbiome of T1D, which can potentially aid treatment, diagnosis and perhaps even prevention.

Fat, Metabolism and Obesity

P3-96

Assessment of cardiac function in obese children and adolescents with metabolic syndrome

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Background: Obesity in childhood and adolescence is often associated with dyslipidemia, hypertension, insulin resistance, inflammation, and disturbances in adipocytokine secretion, which lead to endothelial dysfunction and the development of atherosclerotic cardiovascular disease.

Aim: To determine the prevalence of metabolic syndrome (MS) among obese children and adolescents attending our outpatient childhood obesity clinic, and to evaluate their cardiovascular function.

Methods: One thousand four hundred (n=1400) obese children and adolescents attending our 'Out-patient Clinic for the Prevention and Management of Overweight and Obesity in Childhood and Adolescents' were evaluated and screened in order determine those fulfilling the International Diabetes Federation (IDF) criteria for MS. The study was approved by the local Committee on the Ethics of Human Research. Written informed consent was obtained in all cases by a parent/guardian. All participants underwent clinical examination and standard anthropometric measurements were obtained by a single trained observer. A fasting blood sample for baseline hematological, biochemical and endocrinologic investigations was obtained at 08:00h, and was followed by an oral glucose tolerance test. All subjects underwent echocardiography, ultrasound of the carotid arteries to determine carotid intima-media thickness (cIMT), and a liver ultrasound scan to determine hepatic steatosis.

Results: Seventy seven (n=77) children and adolescents [mean age \pm SD: 13.1 ± 1.9 years; 46 males (59.7%), 31 females (40.3%); 12 prepubertal (14.5%), 65 pubertal (85.5%)] were identified as having MS. Plasma glucose concentrations were 86.7 ± 9.2 mg/dL, serum insulin 34.1 ± 15.8 μ IU/mL, HbA1C $5.3\% \pm 0.2\%$, cholesterol 159.8 ± 30.9 mg/dL, triglycerides 141 ± 63.6 mg/dL, HDL 39.7 ± 8.5 mg/dL, LDL 92.3 ± 27.8 mg/dL, ApoA 125.6 ± 18.7 mg/dL, ApoB 90.9 ± 22.4 mg/dL, Lp(a) 16.99 ± 24.84 mg/dL. The cIMT of the left and right carotid arteries were 0.7 ± 0.2 mm (normal range: 0.49 ± 0.03 mm). Interventricular septal end diastole (IVSd) and systole (IVSs) were 8.8 ± 1.6 mm and 9.9 ± 2.5 mm, respectively. Left ventricular internal diameter end diastole (LVIDd) and systole (LVIDs) were 47 ± 4 mm and 28.8 ± 4.4 mm, respectively, while left ventricular posterior wall end diastole (LVPWd) and systole (LVPWs) were 9.1 ± 2.6 mm and 14.4 ± 4.1 mm, respectively. Hepatic steatosis was identified in 67 (87%) of the participants.

Conclusions: The prevalence of MS in our large cohort of obese children and adolescents was 5.5%. Our findings demonstrate increased cardiovascular risk in children and adolescents with MS.

P3-97

Metabolic Syndrome in adults with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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Introduction: 21-Hydroxylase deficiency is the most frequent form of congenital adrenal hyperplasia (CAH) which is a common autosomal recessive disorder characterized by impaired adrenocortical and adrenomedullary function, and adrenal hyperandrogenism. Chronic glucocorticoid therapy and excess androgen exposure in patients with CAH may predispose them to developing a metabolic syndrome in adulthood. Our objective is to evaluate the metabolic syndrome in adulthood in a Tunisian cohort.

Subjects and Methods: We underwent a prospective study of 26 patients over 16 years of old with CAH.

Results: The cases included 26 patients (M: 11, F: 15) with CAH due to 21-hydroxylase deficiency with a mean age of 27.4 years (16.5-48 years). Eighteen patients had the classical CAH form and the remaining 8 patients had the non-classical form. The mean body mass index was 26.9 ± 4.27 kg/m² (20.3-34.8 kg/m²). The most commonly used drug was hydrocortisone which was used by 21 cases. Five cases had been managed on dexamethasone alone. The mean body fat mass was 17.88 ± 9.8 kg (6-39.3kg) $24.8 \pm 10.65\%$ of body mass (10.9 - 41.6%). Eight patients suffered from obesity. Mean fasting serum glycaemia was 4.82 ± 0.52 mmol/l (3.85-5.54 mmol/l). Eighteen patients (78.2%) had a normal glucose tolerance, whereas 4 patients (17.4%) had impaired glucose tolerance and only one patient had diabetes. A hypercholesterolemia was observed in one patient, a combined hyperlipidaemia in another one and finally a low HDL-cholesterol in 5 patients. Hepatic cytolysis was noticed in one patient with a hepatic steatosis in abdominal ultrasound. Hypertension was confirmed in two patients.

At the end of this metabolic assessment and according to the criteria of theNCEP-ATPIII, the metabolic syndrome was confirmed in a single patient associating android obesity, diabetes and hypoHDLemia.

Conclusion: The risk of developing a metabolic syndrome appears to be considerably increased in case of HCS. All the compounds of metabolic syndrome have been identified during 21-OH deficiency, such as obesity, hyperleptinemia, dyslipidemia, insulin resistance and increasing body fat requiring screening in this population to prevent the complications of those comorbidities.

P3-98

High allostatic load in children with excess of weight

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Objective: Allostatic load (AL) refers to the physiological response that occurs in chronic stress burden. Excessive weight gain is an important source of physiological stress promoting chronic low-inflammation state detrimental for health. We estimated AL score among a pediatric population, in order to define a correlation between cumulative biological dysregulation and excess weight.

Methods: We enrolled 164 children and adolescents (11.89 ± 3.89). According to body mass index (BMI) threshold, the subjects were classified as normal weight BMI<75th percentile; overweight BMI 75-95th percentile; obese BMI>95th percentile. Data based on 16 biomarkers were used to create the AL score. A dichotomous outcome of high AL, was defined for those who had >4 dysregulated components.

Results: High AL was noted in 88/164 subjects (53.65%), without significant difference in sex distribution ($p=0.07$) and pubertal status ($p=0.10$).

The subjects with high AL had a significantly higher BMI ($p<0.001$), WC and WC/HtR ($p<0.001$), triglycerides ($p=0.002$), fasting blood glucose ($p=0.03$), insulin resistance ($p<0.001$), systolic ($p<0.001$) and diastolic blood pressure ($p=0.001$), GGT ($p=0.01$), PCR ($p=0.01$) and calprotectin ($p<0.01$) as well as lower HDL cholesterol ($p=0.002$) than subjects with low AL.

A significant correlation between high AL and overweight/obesity was reported ($p<0.001$). The rate of the cumulative biological dysregulation increased progressively with the increase in BMI categories ($p<0.001$).

Conclusions: high AL was associated with excess weight. AL may be considered a significant contributor correlated to increased morbidity in children with overweight/obesity.

P3-99

Influence of eating habits, sleep patterns and physical activity on anthropometric variables and body composition in children with obesity

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Objectives: The etiopathogenetic of childhood obesity is related to genetic and environmental factors: not only caloric intake or physical activity have an important influence, but also circadian rhythms, including healthy sleep.

The objectives of this study were: a) to analyze the different patterns and duration of sleep, eating habits, meal schedules, time dedicated to exercise and screens of obesity children; b) to evaluate its possible relationship with anthropometric variables and body composition.

Material and Methods: Descriptive Study carried out throughout 2018.

Inclusion criteria: 6-18 years-old children with body mass index (BMI) >2 SDS according to reference tables without any other pathology.

The variables collected were: age, sex, race, weight, height, waist, BMI (Z-Score), fat mass by bioimpedance. Sleep patterns (bedtime and getting up, naps), physical activity, feeding (habits, schedule meals, three-day nutritional registry, frequency of consumption), time of screens and lifestyle questionnaires were also collected. We calculated total daily kilocalories intake, their distribution by macronutrients and the average daily intake schedule.

Results: We studied 90 obese patients (61,1% girls and 38,9% boys) with the following characteristics: 12,7 2,9 years old, BMI (Z-Score) of 3,2 1,2 and waist (Z-Score) of 2,4 0,8. Girls had a percentage of fat mass of 40,3 \pm 5,9% and boys of 37,5 \pm 7,3%.

These patients consumed 1641 304 Kcal per day ($20\pm4,2\%$ proteins, $49\pm4,3\%$ carbohydrates, $31\pm6,4\%$ lipids) distributed as: 22,5 23% at 8,8 1,1 am, 5 \pm 4,7% at 11,5 0,7 am, 36,5 \pm 8,2% at 2,5 0,7 pm, 11 \pm 5,9% at 15,8 1pm and 24 \pm 6,7% at 7,3 1,4 pm. 46% consumed $>10\%$ of day-calories as sugars.

Children slept 8,5 1,2 hours per day on school days and 10,2 1,1 hours on weekends. They spent 2,1 1,6 hours per school day and 4 2,3 on weekend in front of screens. They practiced physical activity 3 2,1 hours per week. 46,5% did not practice any sport out of P.E.

We have to highlight that BMI was positive significantly correlated with a later time and caloric intake at dinner, with the average daily intake schedule and with later time of snack. In addition, a positive correlation with weekend sleeping hours was observed. Conversely, a negative significantly correlation was found with vegetable consumption and kilocalories ingested in breakfast. As expected, most active children had lower BMI than sedentary.

Conclusions: Treatment and prevention of childhood obesity should include not only strategies regarding total caloric intake control and promoting physical activity, but should also consider type of food, meal schedules, caloric distribution along the day and sleep habits.

P3-100

An infant with severe hypertriglyceridemia: Acute and long-term management in the paediatric population

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Background: Severe hypertriglyceridemia, defined as triglyceride concentration greater than 11.2 mmol/L, predisposes to acute pancreatitis, a serious complication with mortality rate as high as 6.5% in children (1). Our case highlights the use of insulin infusion to rapidly lower the triglyceride level and the long term management in a young infant with familial chylomicronemia syndrome (FCS) due to lipoprotein lipase deficiency.

Case Presentation: A 38-day old Chinese girl, born to non-consanguineous couple with normal perinatal history, presented with vomiting and suspected seizure. Examination showed hepatosplenomegaly with no xanthoma. During venesection, milky serum was noted. Blood tests showed triglyceride levels >150 mmol/L and total cholesterol level 23.8 mmol/L. Serum lipase was elevated at 2534 u/L (reference: 23-300 u/L) while amylase level was normal. Computed Tomography of abdomen showed features of acute pancreatitis. Lipoprotein pattern showed a dense chylomicron band while the intensity of the very low density lipoprotein (VLDL) band was mildly increased, compatible with type I hyperlipidaemia. Genetic study for the LPL gene confirmed heterozygous mutation: c.162C>A (exon2), c. 347G>c (exon3), C.835C>G(exon6).

She was kept fasted and started on hyperhydration with intravenous fluid. Triglyceride level dropped to 104 mmol/L after 11 hours of fasting. Intravenous insulin infusion was then started. Triglyceride level decreased slowly to 1.2 mmol/L after 84 hours before the infusion was stopped. Feeding was resumed after one week of fasting with Monogen, a low fat, medium chain triglyceride (MCT) based infant milk formula. She was discharged with normal lipase level and triglyceride level of 2.7 mmol/L.

Weaning diet was started at 6-month of age with low fat diet (fat calorie 15% of total calories). Until the age of 5 years, triglyceride level was maintained at 2.2 to 2.9 mmol/L while high-density

lipoprotein cholesterol (HDL-C) remained low at 0.3 to 0.5 mmol/L. There were no further episodes of acute pancreatitis and she has normal growth and development.

Conclusion: Insulin infusion, together with fasting, resulted in rapid decline in triglyceride level in our patients with no side effects observed in our case. It is thus an effective and safe treatment strategy for paediatric patients with severe hypertriglyceridemia. For the long term management, low-fat diet with fat intake restricted to 10-15% of the total caloric consumption could be effective in patients with lipoprotein lipase deficiency, though compliance can be challenging in children.

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P3-101

BigO: The use of new technologies for the management of childhood obesity – A clinical pilot study

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Background: Obesity represents one of the most challenging public health problems of the 21st century. According to the World Health Organization (WHO), there is a need to create reliable monitoring and behavioral systems, and to investigate their effectiveness in preventing childhood obesity.

Objective: To evaluate a range of novel technologies for collecting photographs, information regarding physical activity and geographic data (GPS) in overweight and obese children and adolescents during their day-to-day life.

Methodology: The study was carried out in the context of the four-year European project BigO (<http://bigoprogram.eu>, Horizon2020, No. 727688). Overweight and obese children and adolescents aged 9-18 years participated in the study following approval by the local Committee on the Ethics of Human Research. Written informed consent was obtained by parents/guardians in

all cases. The data collection system includes the BigO technology platform, which interfaces with a Smartphone and Smartwatch, and records data objectively (using inertial sensors and GPS) for each patient. Data are then transmitted to BigO servers to extract behavioral indicators, including: (a) physical activity/exercise, (b) dietary habits, and (c) environmental conditions (urban, socio-economic, nutritional). During the first pilot phase, participants used the BigO system for 2 weeks to take photographs of the food they consumed, as well as food advertisements, and wore the watch for specific periods during the week (at least 2 weekdays, 1 weekend and 3 nights). Finally, they were asked to return the watch and complete a questionnaire.

Results: Forty children and adolescents aged 9-18 years (11 males, mean BMI \pm SD: 29.94 ± 3.32 kg/m²; 29 females, mean BMI \pm SD 30.86 ± 3.69 kg/m²) participated in the study. All subjects uploaded a total of 571 meal photographs from their mobile camera and recorded 177 days of inertial sensor data from the smartphone or smartwatch (accelerometer). 77% of the participants expressed a positive or neutral opinion when assessing the system.

Conclusions: These novel tools and interventions record the behavior of overweight and obese children and adolescents in an objective way and provide information about their environment. Therefore, they may be useful at designing new public health policies and strategies in order to effectively address childhood obesity.

P3-102

Obesity and Insulin Resistance: Differences between pubertal and prepubertal children

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Introduction: The presence of insulin resistance in obese children is strongly related to severity of obesity. Furthermore, insulin resistance is exacerbated during puberty, mainly due to increased sex steroids and growth hormone secretion.

Objective: To compare obesity and insulin resistance indicators between pre-adolescent and adolescent children.

Methods: 54 pre-adolescent and 41 teenage obese children were analyzed. (51% girls) with an average age of 9.8 ± 2.1 and 11.8 ± 1.8 years respectively. Homeostasis Model Assessment for insulin resistance (HOMA-IR) and Matsuda indices were used as predictors of insulin resistance. After overnight fasting, oral glucose tolerance test (OGTT) was performed and HOMA-IR and Matsuda indices were calculated [Matsuda index: $10000/\sqrt{(FPG \times FIL) \times (\text{mean glucose} \times \text{mean insulin})}$]. Waist circumference, HbA1C, Waist to height ratio and BMI were calculated. Elevated arterial pressure was defined as Systolic Arterial Pressure (SAP) or Diastolic Arterial Pressure (DAP) $\geq 90^{\text{th}}$ percentile. χ^2 and Fisher's exact test methods were used to compare the percentages. Student's t-test was used to compare mean values and linear regression analysis to adjust the results by gender.

Results: Mean BMI was 31.3 (SD=5.5) in the pubertal group and 28.4 (SD=3.5) in the pre pubertal group ($p=0.002$). Glucose levels were similar between the two groups, while greater insulin levels were found in the pubertal group ($p=0.003$) even after adjusting for sex ($p=0.007$). Moreover, the Area Under the Curve (AUC) for insulin was found to be higher in the pubertal group ($p=0.010$). Increased levels of HOMA-IR ($p<0.001$) and lower levels of Matsuda index ($p=0.010$) were found in the pubertal group as compared to the prepubertal group, respectively. Proportion of elevated HOMA-IR was found greater in pubertal subjects as compared to prepubertal ones (70% vs. 32%, $p<0.001$). Furthermore, cases with Matsuda index less than 2.5 were more frequent in the pubertal group (55% vs. 26.9%, $p=0.006$). The aforementioned results were significant after adjustment for gender differences. Waist circumference was found to be increased in the pubertal group ($p=0.003$), however elevated blood pressure, HbA1c and WHtR were not significantly different between the two groups. There were no statistically significant gender differences of all analyzed parameters between the two groups, apart from waist circumference, which was greater in pubertal girls ($p=0.014$).

Conclusions: Insulin resistance is more evident in obese adolescents. Therefore, early childhood obesity needs to be tackled, as insulin resistance increases in adolescence with an increased risk of being persistent in adulthood.

P3-103

Relationship between 25-hydroxyvitamin D with adiposity assessed by body mass index, serum glucose and lipids levels in Korea : a cross-sectional analysis

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Purpose: Vitamin D deficiency is thought to be influenced by cardiovascular function and glucose homeostasis, however the potential influence of vitamin D status on insulin resistance, is not well understood. The aim is investigate the correlations between 25-hydroxyvitamin D[25(OH)D] with adiposity assessed by body mass index(BMI), fasting glucose and lipid levels on schoolchildren.

Methods: From April 2015 to July 2018, 822 patients aged 6 to 18 years who visited the pediatrics outpatient clinics for adolescent developmental evaluation were included. Of the 822 patients, 255 male (31.0%) and 567 female (69.0%) were assessed. According to the vitamin D status, the patients were divided into three groups: under 10 ng/ml, 11 to 20 ng/ml, and over 20 ng/ml, which were classified as the deficiency, insufficiency, and normal group. Logistic regression was used to measure correlations in between 25(OH)D with BMI, serum glucose and lipids levels according to sex and puberty.

Results: Each BMI level according to vitamin D status were 18.1 \pm 3.2 kg/m², 17.6 \pm 3.1 kg/m², and 16.8 \pm 2.9 kg/m², respectively ($p = 0.004$). BMI showed a statistically significant negative linear correlation with 25(OH)D ($\rho = -0.143$, $p = 0.000$). Sex difference of 25(OH)D was significant in girls ($p = 0.04$), but was no significant difference in boys. Difference were found between 25(OH)D and BMI groups in pubertal changes. Furthermore, In accordance with sex and puberty, no correlation were observed between 25(OH)D and blood sugar, or between 25(OH)D and cholesterol.

Conclusions: Higher 25(OH)D levels in children showed lower BMI with a weak negative linear correlation. However, the effect of vitamin D on blood glucose and cholesterol levels was not significant. It seems to be no effect on sex and pubertal changes. Longitudinal studies are to explore whether vitamin D deficiency affect hyperglycemia, hyperlipidemia, insulin resistance and diabetes.

P3-104

Treating Paediatric Morbid Obesity using the Multidisciplinary Intensive Inpatient Approach

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Background: Interplay of various factors contribute to development of morbid childhood obesity and to its recalcitrant nature making it a treatment challenge. A tertiary level, structured multidisciplinary outpatient approach may not always be sufficient in identifying morbid obesity causation. In the absence of other effective treatment modalities, a hospital stay approach can be a suitable option in selected resistant cases.

Methods: We retrospectively reviewed the records of four patients admitted for inpatient obesity management over a 12-month period from March 2018 to February 2019, this being approximately 5% of patients seen. During their stay, they received an individualised multi-modality support, involving inputs from paediatric endocrinologist, obesity nurse specialist, paediatric dietitian, social worker and clinical psychologist. Eating patterns, sleep, behavioural and psychosocial issues were considered. The children were given a guided menu choice from the hospital menu and access to outside food was limited. Regular supervised exercise in the form of hospital walks was encouraged and access to electronic medium was kept to a minimum. Family re-education about obesity and lifestyle modification were reinforced.

Results: Four patients (A, B, C, D) with morbid obesity (average BMI SDS:4.1) were admitted during this period. (Table 1). Mean length of hospital stay was 10.5 days. The prolonged stay of patient C was complicated by life threatening airway obstruction requiring CPAP stabilisation. The average documented weight loss at discharge was 4.9%. Post discharge follow-up at 1 month, BMI SDS losses from admission were sustained in all children.

Table 1. Inpatient stay-Weight,BMI SDS at admission, discharge and follow-up

Patient	Sex	Age (yrs)	Stay (days)	Adm Wt (Kg)	Adm BMI SDS	Disch Wt (Kg)	Disch Wt loss%	Disch BMI SDS	F/u BMI SDS
A	M	11	5	142	4.18	139.8	1.55	4.16	4.15
B	M	13	6	110	3.71	106.6	3.09	3.64	3.64
C	M	9	22	86.5	4.11	77.4	10.5	4.01	3.87
D	F	4	9	35.5	4.4	33.9	4.5	4.14	4.13

Discussion: Supervised intensive multidisciplinary inpatient setting led to demonstration of successful and convincing weight loss. It offers a crucial contact period between the family and multidisciplinary team for re-education and can serve as a guide towards further weight loss. It may identify an at risk home environment if the child regains weight once back home which may warrant care in an alternative environment. Long-term sustainability and feasibility of the inpatient approach is questionable and might add burden on a health system working near maximum capacity already.

Results: In this study, from 528 children 249(47.2%) had more than one cardio metabolic risk factors. Rate of familial history of non communicable diseases was significantly higher in children with cardiometabolic risk factors ($P=0.03, X^2=3.86$). Frequency of tt allele of GCKR(rs1260333) was significantly higher in children with cardiometabolic risk factors than those without it ($P=0.03, X^2=6.50$). Frequency of minor alleles of FADS(rs174547)[tc and cc] was significantly higher in children with cardiometabolic risk factors than those without it (52.6% vs. 44.8%, $P=0.04, X^2=3.21$).

Logic regression analysis regarding the interaction of obesity with studied SNPs in the occurrence of cardiometabolic risk factors provide us 3 Boolean combinations of 7 binary predictor variables. The overall results demonstrated that the interaction of obesity with minor alleles of GCKR (rs1260333) and FADS (rs174547) have an significant role in development of cardiometabolic risk factors.

Conclusion: The current findings support the concept that genetic determinant of diseases could not substantially affect the expression of cardiometabolic risk factors in children, but they could increase the risk by interacting with phenotypes such as obesity or environmental exposure. On the other hand it is also suggested that the differences between obese patients with and without cardiometabolic risk factors may be due to the interaction of several related SNPs with overweight and obesity.

P3-105

The interaction between lipids regulatory genes polymorphism and obesity on cardiometabolic risk factors in children and adolescents

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Objectives: It is suggested that interaction of dyslipidemia related polymorphisms with obesity is one of the possible mechanisms of expression of cardiometabolic risk factors in obese children. In this study, in order to classify high risk obese children and consequently prioritize health care resources for better management of childhood obesity, we investigated the outcome of GCKR(rs780094), GCKR(rs1260333), MLXIPL(rs3812316) and FADS(rs174547) polymorphisms interaction with obesity in the occurrence of cardiometabolic risk factors in Iranian children.

Methods: In this case-control study, 600 frozen blood samples from overweight /obese (n=300) and normal weight (n=300) samples were selected randomly. Demographic and anthropometric characteristics of the selected cases were recorded.

Biochemical measurements of the selected samples were recorded also. Based on recorded data, cases with cardiometabolic risk factors was determined. Allelic and genotypic frequencies of GCKR (rs780094), GCKR (rs1260333), MLXIPL(rs3812316) and FADS(rs174547) polymorphisms were determined in the studied groups. Interaction of studies SNPs with obesity in the occurrence of cardiometabolic risk factors was evaluated.

P3-106

Phenotypic and Genotypic Properties of Children with Suspicion of Monogenic Obesity

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Results: Total of 47 obese patients (20 females, 39 pubertals, mean age of 14.3 years).±3.2 years) were included in the study. Severe obesity present in 85% of patients, early-onset obesity in

51%, consanguinity among parents in 17%, and at least one parent with obesity in 63.8% were present. 55.3% of the patients had a family history of diabetes, 63% had acanthosis nigricans and 77% had striae. Anthropometric and laboratory characteristics of cases are summarized in **Table 1**. In the study, five patient with impaired fasting glucose, five patients with impaired glucose tolerance (one case with MC4R), one with diabetes, 46.8% with high TG, 27.7% with high total cholesterol, 17% with high LDL-K, 14.9% with low HDL-K were determined. Hypertension in 44.7% of the cases and prehypertension in 27.7% of them was observed. Three cases in the study were pathogenic variants in MC4R and in one case heterozygous variant was observed in LEPR which is not considered as pathogen variant. Frequency of sequence variant was 6.3% in the MC4R gene, and frequency of the sequence variant in the LEPR gene was 2.1%. Clinical and demographic characteristics of cases with sequence variants is summarized in **Table 2**.

Conclusion: In this study, a sequence variant ($n=4$) was determined in 8.5% of children examined for suspicion of monogenic obesity. In all cases with sequence variant, obesity developed in the first year of life. Monogenic obesity should be investigated in presence of severe obesity in the first year of life, consanguinity and obesity in parents.

P3-107

Relation of serum 25 hydroxy-vitamin levels D3 with body-mass index in pediatric patients

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Background: The aim of our study is to determine the relation of vitamin D levels (25(OH)VD) with body-mass index (BMI), age and month of extraction in pediatric patients.

Materials and Methods: We present a retrospective review of medical records of patients under 18 years of age visited by the Children's Endocrinology Service (overweight and obesity) and ambulatory pediatrics (healthy and normal weight children) at our hospital between June 2016 and June 2018. We examined 176 medical records and made a correlation analysis in all parameters. We classified our patients according to their BMI and compared their 25(OH)VD levels (Chemiluminescent Immunoassay) with their BMI, age and month of extraction. The cut-off points of 25(OH)VD used are the ones suggested by Holick.

Results: The medical records of 176 patients (women:93/ men:83) were reviewed, mean age: 10.2 years, 95%CI:9.5-10.9. Of the total of 25(OH)VD determinations obtained, we observed levels of sufficiency (≥ 30 ng/ml) in 33.5% patients, insufficiency in 43.2% (20-29 ng/ml) and deficiency in 23.3% (< 20 ng/ml). We detected significant negative relationship between 25(OH)VD and BMI ($r: -0.227$, $p: 0.003$), and between 25(OH)VD and age ($r: -0.273$; $p: 0.000$); and significant positive relationship between 25(OH)VD and month of extraction ($r: 0.2354$, $p=0.001$), increasing levels during summer months (August, average: 49.8ng/ml, 95%CI:15-110) and decreasing during winter (January, average:

21.3ng/ml, IC95%: 16-26.7). There is also a progressive fall in values of 25(OH)VD since 10.5 years of age (mean: 24.1 ng/ml, 95% CI: 18.3-29.8).

Conclusions: These results suggest that there is an inverse association between BMI and 25(OH)VD levels. Vitamin D decreases significantly during winter and from the beginning of puberty, moment of great vulnerability due to the fact that the maximum peak of corporal growth takes place.

P3-108

Vitamin B12 Levels in Children After Metformin Treatment

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Background and Aims: Vitamin B12 is an essential micronutrient required for optimal hemopoietic, cardiovascular and neurocognitive functions. There are some literature data that Metformin induces vitamin B12 malabsorption, which may increase the risk of developing vitamin B12 deficiency and subsequently elevation of homocysteine levels. High concentrations of homocysteine has been associated with higher risk of coronary artery disease, arterial hypertension, hip and other bone fractures, rheumatoid arthritis, diabetes, and other serious chronic diseases. As first line therapy, Metformin is the most frequently prescribed medication in cases of hyperinsulinism and type 2 diabetes. It is one of a few antihyperglycaemic agents, associated with improvement in cardiovascular morbidity and mortality. Metformin acts by reducing the amount of glucose, produced by the liver, as well as increasing patient's sensitivity to insulin.

Methods: Twenty five children with obesity aged between 10 and 17 years were included in the study. Levels of B12 and homocysteine were measured in the participants. All of them had BMI > 97th centile. Oral glucose tolerance test was performed and hyperinsulinism was diagnosed in the children. The patients were treated with Metformin 850 mg twice daily for a period of 1 to 3 years.

Results: Ten patients had levels of B12 within the laboratory reference range and recommended homocysteine concentration $< 7.2 \mu\text{mol/l}$. In 15 of the participants we found insufficient levels of vitamin B12 $< 200 \text{ pg/ml}$ and elevated homocysteine levels.

Conclusions: Our results are consistent with literature data that Metformin is associated with low levels of vitamin B12. These are the first results of an ongoing study in our department. We recommend that vitamin B12 levels should be assessed regularly in patients treated with Metformin longer than a year.

P3-109**Follow-up evaluation of clinical markers and inflammatory, biochemical and hormonal profiles in children with bodyweight problems**

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Introduction: In the last years, the relationship between clinical markers and blood parameters has been evaluated closely as part of transversal studies, but a longitudinal approach might be more useful in explaining its complexity.

Aim: The study aims to evaluate the relationship between changes in the values of clinical markers and of the inflammatory, biochemical and hormonal profiles of obese and overweight children over a 4 to 12-month period.

Materials and Methods: An observational retrospective study was conducted on obese and overweighed children evaluated from January 2017 to March 2019 in the First Pediatric Clinic from Cluj-Napoca, Romania. Children without any comorbidity evaluated more than once in this period were included in the analysis. A minimum 4-month follow-up period was established. Clinical markers (body mass index, waist circumference, blood pressure) and inflammatory markers (leucocytes and neutrophils counts, C-reactive protein), biochemical serum markers (liver enzymes, uric acid, glycemic and fat profiles), insulin and cortisol levels were obtained from medical files.

Results: The study included twenty-two patients aged between 2 years and 17 years among which 20 were obese ($\geq 95^{\text{th}}$ percentile) and 2 overweight ($\geq 85^{\text{th}}$ percentile) at the initial evaluation. The follow-up body mass index (BMI) decreased in 12 cases without reaching statistical significance.

The fasting glucose levels significantly decreased at the follow-up as compared to baseline assessment (P -value = 0.010) within the normal range limits. There was a significant increase in fasting insulin levels (baseline median = 14.9 kg vs. follow-up median = 20.5 kg, P -value= 0.05, n=11). Moreover, there was a positive correlation between bodyweight and insulin levels in both baseline ($p=0.60$, P -value= 0.051, n=11) and follow-up ($p=0.53$, P -value= 0.028, n=17) assessments. One patient had hyperinsulinemia at baseline evaluation and 6 developed it at follow-up. Neither the change in glycemia, nor in the insulinemia correlated to changes in BMI or percentiles (P -value > 0.05). There was no significant difference or correlation between baseline and follow-up measurements regarding other parameters.

Conclusion: Fasting glucose and insulin levels changed significantly during the follow-up period independently of body mass index and HOMA-ir variations. Fasting hyperinsulinemia may precede the changes in body mass index as insulinemia is a sensitive indicator of lipid and carbohydrate metabolism. In addition to reflecting the effect of insulin, the glycemic profile may also reflect the mechanisms leading to insulin resistance onset. A longitudinal prospective study would explain the relation between clinical and laboratory markers in obesity more clearly.

P3-110**Gastroduodenopathies in obese young people**

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Aim: To study of the pathology of the upper gastrointestinal tract in obese young people.

Materials and Methods: 87 young people with primary obesity (body mass index above 30 kg/m^2), 40 boys (45.9%), mean age 17.9 \pm 2.2 years (group 1) were under observation. Conducted clinical, laboratory and instrumental examination, esophagogastroduodenoscopy, Ph-metry and determination of H.Pylori infection. The 2nd group consisted of 43 patients with gastroduodenal pathology without obesity. The control group consisted of 30 healthy people. Patients 2 and the control group did not differ in age and sex from patients in group 1. All patients were tested for blood leptin levels. Statistical processing of the data was performed using the STATISTICA for Windows system, using the Mann-Whitney test.

Results: Clinical symptoms of lesions of the upper gastrointestinal tract were found in 82.7% of the 1st group. Abdominal pain occurred in 67.8% of patients. 32.2% did not have abdominal pain, however, periodic symptoms of dyspepsia are characteristic. Aerophagia was found in 21.8%, in 6.9% - increased saturability and a feeling of heaviness in the right hypochondrium after eating. In 24.1% of the manifestations of gastroduodenopathy were minimal and non-permanent. Symptoms of dyspepsia were observed mainly in young people with a long term obesity. Esophagogastroduodenoscopy revealed approximately half of the patients had chronic gastritis, 19.5% had chronic gastroduodenitis, and 9.2% had chronic gastritis with erosive bulbit. Increased secretion of gastric juice was noted in 41.4%, decreased - in 21.8%, in 2.3% - normal. The urease test was positive in 52.9% patients of the 1st group and 48.8% of the 2nd group. The results of the survey showed a significant difference ($p < 0.05$) in the severity of gastroduodenopathy symptoms in patients with obesity compared with patients in group 2. The level of leptin in group 1 was significantly different for the worse from patients of group 2 and healthy subjects.

Conclusion: In 41.4% of young people with obesity, gastroduodenopathy was seen as a chronic gastritis with increased secretory function. In 52.9% young obese people H.Pylori plays the leading role in the genesis of gastroduodenopathy. A significant increase ($p < 0.05$) in the level of leptin in patients with obesity in combination with gastroduodenal pathology was found, most pronounced in young people with H. Pylori compared with patients with gastroduodenopathy without obesity and healthy people.

P3-111

Seven Methods of indicating childhood Metabolic Syndrome

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Introduction and Aims: Metabolic syndrome (METs) has different complications such as cardiovascular diseases and diabetes type 2. There is no uniform definition for METs. In this study, we aimed to define METs from different viewpoints to determine the most appropriate method that could be used for early METs diagnosis in general population and treat them immediately.

Materials and Methods: This study was an analytic cross-sectional study which was conducted on 725, twelve year-old-girls and boys from Rasht city in Iran. METs was defined based on 7 different methods.

Results: In this study, 725 students included 247 (34.1 %) female and 478 (65%) male. Results showed that 85.1% were normal weight, 4.83% overweight, and 10.7% obese. The highest and lowest percentages of METs were obtained by DE Ferranti (17.5%) and viner et al (0.8%) methods, respectively. Result showed that viner et al., had the highest degree of agreement with NCEP ATPIII and the lowest with DE Ferranti. Furthermore, De Ferranti showed the highest degree of agreement with NHANESIII and the lowest with Viner et al.. There was a significant relation between the prevalence of METs and obesity by all methods.

Conclusions: According to results, the identification of the cut off points of obesity could help to promote public health care.

P3-112

Insulin resistance in children and adolescents with exogen-constitutional obesity

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Objective: evaluate insulin resistance (IR) in children and adolescents with exogen-constitutional obesity (ECO) depending on the stage of sexual development.

Materials and research methods: 100 children and adolescents with ECO of the UzBek population from 6 to 16 years were observed (mean age 11.7 ± 0.25 years). The control group consisted of 71 healthy children of the appropriate age (mean age 11.1 ± 0.33 years).

All children and adolescents were evaluated: anthropometric indicators. The criteria for overweight and obesity in children were determined according to the percentile BMI tables (WHO 2007). The level of fasting immunoreactive insulin (IRI) using the RIA method. IR indicators were calculated using the following HOMA formulas (HOMA-IR Index Homeostasis Model Assessment).

Results and discussion: It is established that the analysis of the fasting IRI level in the control group did not reveal a significant

difference from the stage of sexual development and gender. Boys and girls with ECO, regardless of the sexual development stage, the indicator of fasting IRI was above control.

The HOMA-IR index is significantly higher in patients with ECO than in healthy children, regardless of gender and sexual development stage. IR (NOMA values > 97 per.) were detected in IVF, respectively, in 44.4% and 18.2% of boys and girls with a stage of sexual development 1 according to Tanner. In adolescents (65.5% - boys and 40.9% - girls), cases of HOMA > 97 peppers were also detected in the initial puberty stage. 68.8% of boys and 61.5% of girls with 4-5 stage according to Tanner had an index BUT-MA > 97 per. It should be noted that such values were more common in boys than in girls at all stages of sexual development.

Conclusions: Thus, the conducted studies that HOMA values > 97 per. were more common in boys than in girls at all stages of sexual development. In children with obesity, dysmetabolic disorders associated with IR, matters as the main component of the metabolic syndrome. The study of glycemia and IRI on an empty stomach with the calculation of HOMA-IR should be mandatory for children with progressive obesity.

P3-113

Severe Hypernatremia Revealing a ROHHAD-NET Syndrome

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Introduction: Rapid-onset Obesity with Hypoventilation, Hypothalamic dysfunction and Autonomic Dysregulation (ROHHAD) recently named ROHHAD-NeuroEndocrine Tumors (ROHHAD-NET) syndrome is a rare cause of obesity in children. The diagnosis is challenging and can easily be confused with other causes of obesity.

Case Report: We report a case of a six-year-old boy, referred to our clinic for hypernatremia. Six months ago, he started to present episodes of acute respiratory distress diagnosed as asthma. A few months later and following acute respiratory distress, he was admitted for coma due to a severe hypernatremia reaching 200 meq/l complicated by renal failure. He was successfully managed and left the intensive care unit with a normal electrolyte balance and a normal renal function. Parents reported progressive weight gain without polyphagia and physical examination showed obesity with a BMI of 23 (> 97thcentile), normal height, respiratory distress, excessive sweating and Raynaud Phenomenon. The child had normal intellectual development with good school performance and no psychiatric disorders. ROHHAD-NET Syndrome was suspected and further investigations showed Hyperprolactinemia: 91.4 ng/ml (3.7-17.9), megaloblastic anaemia, obstructive sleep apnoea and a restrictive alveolar syndrome. No pituitary deficiency was detected and thoraco-abdominal CT Scan showed calcifications in the right adrenal which was slightly enlarged. Vanyl Mandelic Acid

was normal $3.98\mu\text{mol}/\text{mmol}$ ($N<10$) as well as adrenal steroids: SDHEA: $0.28\mu\text{g}/\text{ml}$ (0.24-2.1); $\Delta 4$ Androstenedione: $0.3\text{ ng}/\text{ml}$ (0.01-1.31); testosterone $<0.05\text{ ng}/\text{ml}$ (0.39-2.01). Ganglioneuroma is suspected for which further investigations are being done. Fluid balance is well controlled with oral hydration and low sodium diet. Obesity is managed by dietary changes alone since exercising remains limited by the respiratory distress episodes.

Conclusion: Our patient's management requires a multidisciplinary team collaboration and his prognosis relies on the severe hypernatremia episodes, the sleep apnoea disorder and the development of neuroendocrine tumours.

P3-114

Rare Case of Acquired Generalized Lipodystrophy in A 14-Year Old Patient

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Background: Lipodystrophies are a group of rare disorders characterized by varying degrees of body fat loss. The metabolic abnormalities associated with lipodystrophy include insulin resistance, often leading to diabetes mellitus, hypertriglyceridemia that may be severe enough to cause acute pancreatitis and hepatic steatosis that may lead to cirrhosis.

They can be either genetic or acquired, generalized or partial. Acquired generalized lipodystrophy (AGL) is more common in females, usually appears before adolescence, is characterized by progressive loss of fat affecting the whole body but some fat accumulation can appear in the face, neck, axilla. Metabolic complications are frequent. AGL is often associated with autoimmune diseases.

Objectives: We report a case of a 14-year old female presenting with very low body-fat tissue, with increased muscle tissue at the trunk, upper and lower extremities. The adipose tissue is present in the face and the neck, causing a „buffalo-hump” appearance. She also presented acanthosis nigricans at bilateral axillary level and posterior region of the neck. The patient had normal fat distribution during childhood, followed by onset of progressive fat loss around late childhood.

Method: Laboratory findings showed a very low level of leptin (Leptin= $2.8\text{ng}/\text{ml}$, $N:>12\text{ng}/\text{ml}$), hyperinsulinism (Insulin= $65.3\text{uUI}/\text{ml}$, $N: 6-27\text{uUI}/\text{ml}$). Blood glucose levels, triglycerides and liver enzymes were within normal levels at presentation. The patient also presented with thyrotoxicosis with elevated TRab.

Results: Given the clinical appearance of the patient, the very low level of leptin and the association with Graves Disease, the diagnosis of acquired generalized lipodystrophy is the most likely. For the hyperthyroidism the patient was started on antithyroid agent (30 mg Thyamasole) and Metformin was started for her progressing hyperinsulinism. Consequently to normalization of her thyroid function, cholesterol and triglycerides values started to increase. One year after starting antithyroid medication and 3 months after starting metformin she presented increased liver enzymes and was evaluated for autoimmune/infectious hepatitis and non-alcoholic fatty liver disease, but none was confirmed.

Also, given the very low level of leptin, the patient can be a good candidate for treatment with metreleptin.

Conclusion: We present the case of a young female with AGL with late childhood onset of disease, typical clinical presentation of fat loss, very low leptin levels and insulin resistance from a young age, while also associating Graves' disease.

The association of Graves' hyperthyroidism and its therapy with AGL influences the evolution of AGL metabolic consequences and comorbidities.

P3-115

Gender-based differences in the clustering of metabolic syndrome factors in children and adolescents

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Background: We depicted gender-differences in metabolic syndrome (MS) clustering before and after puberty in pediatrics, to identify early childhood prevention intervention and treatments.

Methods: We considered 1079 children and adolescents. According to body mass index (BMI) percentiles the subjects were classified as normal weight BMI $<75^{\text{th}}$, overweight BMI 75-95 $^{\text{th}}$ and with obesity BMI $>95^{\text{th}}$. MS was diagnosed when 3 of the following criteria for age and sex percentiles were met: BMI $<95^{\text{th}}$, tryglicerides level $>95^{\text{th}}$, HDL-cholesterol level $<5^{\text{th}}$, blood pressure $>95^{\text{th}}$ percentile, fasting blood glucose $>100\text{ mg/dl}$ and/or HOMA-IR $>97.5^{\text{th}}$ percentile.

Results: The prevalence of dismetabolic factors was similar in both genders, except for pathological BP, higher in males ($p=0.02$). MS was detected only in patients with obesity, with an higher prevalence in pubertal than pre-pubertal subjects ($p=0.01$), without any significant difference between gender. In prepuberty, the most common MS combination was obesity (HBMI)+hypertension (HBP)+hyperglycemia/insulin resistance (HGLY/IR) followed by HBMI+low HDL-levels (LHDL) + HGLY/IR versus HBMI+HBP+HGLY/IR followed by HBMI+HBP+LHDL respectively in females and males. In pubertal period, the combination HBMI+HBP+LHDL+ HGLY/IR was present in both genders.

Conclusion: we confirm that MS is an important consequence related to obesity, particularly in post-puberty stage. Some gender-based differences may be early considered in order to define specific preventive and treatment strategies.

P3-116**Fat mass index and fat-free mass index percentiles in healthy Spanish adolescents**

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Background: Body mass index not allow to discriminate the proportional composition of the different body compartments: fat mass and fat-free mass.

Objective: The aim of this study is to elaborate standardized values of the fat mass index (FMI) and fat-free mass index (FFMI) in healthy adolescents (both sexes) using anthropometric techniques in order to be available as reference standards in daily clinical practice.

Subjects/Methods: Transversal study in 940 healthy Caucasian adolescents (370 males and 570 females), aged 10.1 to 14.9 years. Weight, height, skinfold thickness (biceps, triceps, subscapular and suprailiac) were registered, and body mass index (BMI), percentage of total body fat, FMI and FFMI, and percentile distribution of FMI and FFMI were calculated.

Results: In males a progressive increase ($p<0.05$) in the FFMI is observed (10 y: 13.8 ± 0.7 vs. 14 y: 15.6 ± 0.7), and the percentage of total body fat (10 y: 25.4 ± 5.8 vs. 14 y: 22.4 ± 5.9) and FMI (10 y: 4.8 ± 1.4 vs. 14 y: 4.3 ± 1.5) progressively decreased ($p<0.05$). In contrast, in females the percentage of body fat mass (10 y: 27.4 ± 5.9 vs. 14 y: 29.3 ± 3.5), FMI (10 y: 5.1 ± 1.4 vs. 14 y: 6.2 ± 1.2) and FFMI (10 y: 13.4 ± 0.8 vs. 14 y: 14.7 ± 0.9) progressively increased ($p<0.05$). Except for the 10 years, FMI was significantly higher ($p<0.05$) in females with respect to males in all ages. FFMI was significantly higher ($p<0.05$) in males in all ages. Percentile distributions of FFMI and FMI for healthy adolescents (both sexes) categorized by age are displayed.

Conclusions: Standardized values of fat mass index and fat-free mass index would be a very useful instrument for the diagnosis and analysis of body composition changes during the treatment of childhood obesity.

P3-117**Comparison of Different Criteria for the Definition of Insulin Resistance and Its Relation with Metabolic Risk in Overweight and Obese Adolescents**

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This study aimed to compare cut-off points corrected for age and gender (CCOP) with fixed cut-off points (FCOP) for fasting plasma insulin and homeostasis model assessment-insulin resistance (HOMA-IR) for the diagnosis of IR in Korean obese children and adolescents and to identify IR applying CCOP and FCOP using as outcome the presence of dyslipidemia and Metabolic syndrome (MetS).

We performed a cross sectional analysis of data from 195 adolescents aged 12-18 years who participated in Korean National Health and Nutrition Examination Survey (KNHANES, 2009-2010). Overweight and obese individuals were defined by BMI z score ≥ 1 . IR was defined as two criteria: FCOP and CCOP.

The prevalence of IR using HOMA-IR in FCOP and CCOP was 105 (53.8%) and 53 (27.2%) respectively. The prevalence of IR using fasting plasma insulin was 120 (61.5%) of FCOP and 79 (40.5%) of CCOP. Dyslipidemia, abdominal obesity and MetS were not associated to FCOP or CCOP. Fasting blood glucose remained in normal ranges in all patients with IR.

More cases of IR were detected in FCOP of plasma insulin or of HOMA-IR compared to the CCOP, but were not associated with incidence of metabolic disease. There is no fluctuation of blood glucose in this age group, even though presence of IR, and there is no significant difference in fasting plasma insulin between IR detected by HOMA-IR and by fasting insulin.

P3-118**Somatostatine Analogue in Hypothalamic Obesity**

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Hypothalamic Obesity (HyOb) is the most flagitious endocrinologic problem following surgical intervention for childhood brain tumors. There is still no curative therapy for HyOb.

A 4y 10/12 m old girl presented with headache and vomiting. Pituitary MRI revealed a craniopharyngioma and she was operated. The replacement therapies for postop panhypopituitarism was given but she developed HyOb within 4 months after operation (table-1). Somatostatin analogue (SA) (octreotide, 10 mcg/kg/d) was initiated at 6.months of postop period due to hyperinsulinism in OGTT and also GH treatment was added (table-2). Although, she was diabetic and still hyperinsulinemic in 1 year later OGTT, octreotide demonstrated significant reduction in BMI SDS (table-1, 2). Since she had normal HbA1c and normoglycemia in blinded CGM except one value, octreotide octreotide-LAR was switched (7.5 mcg/kg/d). As a side effect, a gall calculi was developed 4 months later, ursodeoxycholic acid was added. But the octreotide-LAR was stopped at 6.months due to suspicion of acute cholecystitis. After 3 months, she had kept same weight with BMI SDS reduction (table-1).

SA might be still an option in some selected patients with HyOb. Although the reason of using SA in HyOb is hyperinsulinism, this case showed that hyperinsulinism still continue under successful SA therapy with delayed insulin peak.

Table-1

	Preop	4.months	6.months	18.months	24.months	27.months
Height SDS	-0.1	-0.2	0.1	1.45	1.75	1.8
Weight SDS	0.6	3.4	4.6	4.1	3.5	3.3
BMI SDS	0.9	3.8	4.4	3.3	2.9	2.7
HyOb therapy			Octreotide	Octreotide-LAR	stopped	

Table-2

GHST GH (ng/ml)	First OGTT		Second OGTT (30.min later octreotide injection)	
	Glucose (mg/dl)	Insulin (mcU/ml)	Glucose (mg/dl)	Insulin (mcU/ml)
0.min	<0.05	82	15	88
30.min	<0.05	174	164	150
60.min	<0.05	161	186	218
90.min	<0.05	158	251	286
120.min	<0.05	125	175	259
180.min				161
				302

P3-119**ESPE 2019. Physical Activity, Food and Metabolic Risk in Children and Adolescents**

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Introduction: The incidence of obesity increases unstoppably in all populations and at all ages, and with it, the associated metabolic morbidity and mortality. The promotion of physical activity and a healthy diet are the fundamental elements to alleviate this situation. The objective of this study is to determine the relationship of physical activity and eating patterns with body composition, the degree of adiposity and certain metabolic risk factors.

Material and Methods: An observational epidemiological study with a cross-sectional design in 813 patients between 6 and 14 years of age who attend child nutrition and / or endocrinology clinics in 4 Spanish hospitals at the third level, where physical activity and diet patterns are evaluated through questionnaires. compare with body composition and adiposity results through anthropometry and DEXA. The statistical analysis is done with the SPSS package.

Results: Moderate and vigorous physical activity presented negative correlation with the percentage of total fat body composition we observed a negative correlation between moderate activity and the ($p<0.0001$), and vigorous activity and percentage of total fat ($p=0.003$). As far as the percentage of lean mass is concerned, it increases significantly with the practice of physical activity ($p<0.0001$). Overweight children are those who have a better compliance with the recommendations of the disadvised foods ($p=0.001$). Patients are grouped into three clusters according to four variables for the joint study of physical activity and diet: recommended foods, disadvised foods, moderate and intense physical activity. A significantly higher percentage of normal weight belong to the cluster 3 (higher level of physical activity and compliance with recommended food recommendations but not those disadvised foods), compared to children with overweight and obesity ($p=0.038$). We can also observe that in cluster 2 (better compliance with nutritional recommendations and physical activity level below the recommendations), it is children with normal weight who are in a lower percentage than those who are overweight and obese ($p=0.038$). The children in cluster 3 presented significantly higher levels of HDL cholesterol ($p=0.028$) and greater total lean mass and lower percentage of total fat mass ($p<0.0001$). Insulin and HOMA-IR index are also lower in cluster 3, although they do not show significant differences.

Conclusions: The combination of frequent physical activity and healthy diet is related to a lower degree of adiposity and an increase in HDLc levels, which causes a decrease in metabolic risk.

P3-120

Toward a simple marker of hepato-visceral adiposity and insulin resistance: the Z-score change from weight-at-birth to BMI-in-childhood

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Insulin resistance and hepato-visceral (central) fat excess are thought to contribute to an earlier timing of adrenarche/pubarche and puberty/menarche; this earlier timing in turn relates often to a mismatch between pre- and postnatal weight gain, which can be estimated by calculating the Z-score change from birth weight (BW) to body mass index (BMI) in childhood. We tested the hypothesis that this calculation may serve as a proxy of insulin resistance and hepato-visceral adiposity in prepuberty by reappraising a cohort of children (mean age, 8.5 years), born appropriate- (AGA, n=41) or small-for-gestational age (SGA, n=45), followed since birth (n=76) or age 3 years (n=10). Assessments included anthropometry, fasting glucose, insulin, liver volume, and hepatic fat, subcutaneous and visceral fat in the abdominal region (by MRI). Z-score change BW-BMI closely associated to central fat ($R=0.74$; $p<0.0001$) and insulin resistance ($R=0.71$; $p<0.0001$). This results suggest that Z-score change BW-BMI could be viewed as a simple candidate-marker for hepato-visceral adiposity and insulin resistance in prepubertal children.

P3-121

Associations between lipid parameters and insulin resistance in obese adolescents

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Background: Non-communicable disease epidemic is directly related to the dislipidemia and insulin resistance (IR) that associated with acute cardiovascular events. Meanwhile, there is not much has known about interrelation between this parameters in pediatric patients.

Purpose: of the study is to analyze associations between lipids and insulin resistance so as to screen high risk subjects during adolescence.

Subjects and Methods: 215 adolescents (mean age is 14.03 ± 2.21 y.o) with no gender difference were examined. Lipids assessment included measurement of total cholesterol (TC), triglycerides (TG), low density lipoproteins (LDL), high density lipoproteins (HDL). Guideline on the management of high blood

cholesterol (ACC, 2018) was used for distributing lipid parameters by the groups: acceptable, borderline and abnormal (high). Insulin resistance (IR) was analyzed by HbA1C level, fasting glucose (FG) and fasting insulin (FI) measurement followed by HOMA-IR calculation. Fasting status (at least 8 hours) was required. Standard statistics (SPSS soft) used for the data analysis.

Results: We have established that about half (46,51%) of obese adolescents have acceptable TC level, about one third (29,30%) - borderline and just quarter of them (24,19%) were hyperlipidemic.

TG are high in 48,15%, borderline in 40% and acceptable just in 11,85%. HDL are borderline low in 84,61%, acceptable in 3,07% and high in 12,32%.

LDL are acceptable in vast majority of overweight (77,90%) with the equal distribution of borderline and high results (by 11,05%).

Increasing of TC is associated with FG (4,61; 4,74; 5,20, $p=0,003$), FI (24,06; 25,31; 29,28, $p=0,02$) and HOMA-IR (3,90; 4,94; 5,67, $p=0,003$), HbA1C (6,23; 6,62; 7,13, $p<0,05$)

Increased TG are associated with HOMA-IR (5,46; 5,14; 6,46, $p=0,02$) and C-peptide (3,43; 2,99; 4,81, $p<0,01$), HbA1C (5,76; 6,53; 6,97, $p<0,05$)

Increasing of LDL is associated with HOMA-IR (4,26; 5,13; 7,82, $p<0,01$), FI (25,07; 23,80; 33,83, $p = 0,01$)

Decreasing HDL is associated with HOMA-IR (2,26; 5,96; 5,86, $p=0,003$)

Conclusions:

- Just one forth of obese children is hyperlipidemic, whereas dislipidemias with high TG and borderline HDL are common.
- Fasting relationships between FG and FI (by HOMA-IR) are crucial for all lipid parameters shift in obese adolescents. Moreover, seems, insulin sensitivity drop down could b causative for the HDL decline.
- Hyperlipidemia and high TG are related to the diabetes mellitus

P3-122

The Characteristic of Thyroid Status in Overweight and Obese Young People with Insulin Resistance

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Introduction: Due to the widespread occurrence of both obesity and hypothyroidism, physicians need to be especially attentive to the possible thyroid dysfunction in obese patients. The relationship between thyroid hormones and obesity in combination with insulin resistance in young people is not fully understood.

Materials and Methods: In order to study of thyroid status in young people with overweight and obesity in combination with insulin resistance 68 patients $16 \pm 2,1$ y.o. were examined. 32 - overweight - group 1 and 36 - obese - group 2, HOMA insulin resistance index above 2.77. Control group were 15 healthy adolescents. Ultrasonography of the thyroid gland, TSH, free thyroxine (fT4.), free triiodothyronine (fT3), thyroglobulin antibodies and AT-TPO were carried out. Statistic analysis was made using the program Statistica (ver 2009 for Windows), criteria Mann-Whitney, Wilkinson and χ^2 .

Results and Discussion: On thyroid ultrasonography the enlargement of size and echogenicity change of thyroid tissue ($p>0.05$)

were established. In the 1 group nonsignificant ($p>0.05$) increase of TSH were found. In 2 group the concentration of fT4 was significantly reduced and a TSH was significantly increased ($p<0.05$). The nonsignificant increase ($p>0.05$) of AT-TPO in patients who are overweight and a significant ($p<0.05$) in patients with obesity were established. This trend did not concern to thyroglobulin antibodies. Positive correlation between the concentration of TSH and BMI and insulin resistance index HOMA-IR was registered. It was also established correlative relationship between SH, leptin and adiponectin. Significantly lower concentrations of adiponectin are detected in patients of 2 group compared with the 1 group and the control group, respectively $6,1 \pm 3,9$ mkg/ml, $8,9 \pm 4,2$ mkg/ml and $17,1 \pm 4,9$ mg/ml ($p <0.05$). In 22.7% of young people with obesity and insulin resistance recorded a significant increase in thyroid stimulating hormone combined with relative reduction of free thyroxine, which is the sign of hypothyroidism.

Conclusion: Revealed thyroid insufficiency, combined with the stimulation of antibody production is probably one of the mechanisms of development and progression of not only obesity, but also insulin resistance in young people, dictating the need for its early detection and appropriate correction.

P3-123

Validity of non-high-density lipoprotein cholesterol for detecting dyslipidemia among Korean adolescents

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Objectives: Non-high-density lipoprotein (HDL) cholesterol is an alternative method to assess dyslipidemia and is not required fasting. We aimed to assess the validity of non-HDL cholesterol for detecting dyslipidemia among Korean adolescents.

Subjects and Methods: Data for 6,989 adolescents aged 10 to 19 years (3,684 boys and 3,305 girls), were obtained from the Korean National Health and Nutrition Examination Surveys during 2008-2016. Dyslipidemia was defined by having one of the followings; total cholesterol ≥ 200 mg/dL, triglyceride ≥ 130 mg/dL, low-density lipoprotein (LDL) cholesterol ≥ 130 mg/dL, or HDL cholesterol <40 mg/dL. Non-HDL cholesterol ≥ 145 mg/dL was used to detect dyslipidemia based on National Heart, Lung, and Blood Institute 2011.

Results: The overall prevalence of dyslipidemia were 27% and 37% among Korean adolescents based on calculated and measured LDL cholesterol level, respectively. The prevalence of non-HDL cholesterol level ≥ 145 mg/dL were 7.1% and 8.5% in teenage boys and girls, respectively. High non-HDL level were found in 97.1% and 97.7% of teenage boys and girls with dyslipidemia, respectively. The odds ratio for having dyslipidemia in adolescents with high non-HDL cholesterol level compared with normal level were 75 and 112 in teenage boys and girls, respectively. High non-HDL cholesterol level especially detected 96.3% and 95.2% of high measured LDL-cholesterol level in teenage boys and girls ($P<0.001$

and $P<0.001$, respectively). Prevalence of having parental history of dyslipidemia were similar whether adolescents had high non-HDL cholesterol level or not ($P=0.640$ and $P=0.506$, respectively).

Conclusions: Non-HDL cholesterol appeared to be a reliable dyslipidemia screening test also in adolescents and easily calculated from random sample not required fasting.

P3-124

Early Onset Monogenic Obesity: Two Cases with Homozygous Mutation in Lepr Gene

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Introduction: Although the majority of the cases with obesity have a multifactorial etiology, rare monogenic forms of obesity exist. Several genetic disorders have been described that lead to early onset monogenic obesity. Leptin (LEP), leptin receptor (LEPR), melanocortin 4 receptor (MC4R), proprotein converting protein subtilisin / kexin-type 1 (PCSK1) and proopiomelanocortin (POMC) are the genetic mutations that have been most frequently shown to cause monogenic forms of obesity. In this study, we aimed to present two cases who applied with early onset morbid obesity and hyperphagia in whom we detected homozygous missense and homozygous frameshift mutations in LEPR.

Case 1: A 6-month-old girl presented to our outpatient clinic with morbid obesity. In physical examination; body height was 71.1 cm (+1.61 SDS), body weight was 13.1 kg (+4.76 SDS), body mass index (BMI) was 25.9 (+4.4 SDS). Her birth weight was 3600 g. The parents were first degree cousins. She had hyperphagia and rapid weight gain at the age of 3 months. She had no red hair. In molecular analysis; C.1938G> T (p.W646C) variant and C.946C> A (p.P316T) homozygous missense mutation in the LEPR gene were detected. In the molecular analysis of the family, both parents and her sibling have been shown to be heterozygous for the same gene.

Case 2: A girl with a birth weight of 3250 g was admitted with hyperphagia and excessive weight gain at 8 months of age. There was a consanguinity (first cousin marriage) between his parents and she had a height of 73 cm (+1.21 SDS), her weight was 19.8 kg (+7.94 SDS), her BMI was 37.1 (+6.9 SDS). In molecular analysis; homozygous novel c.1220-1221insT frameshift mutation was detected in the LEPR gene. In the molecular analysis of parents; both parents were shown to be heterozygous carriers.

Conclusion: Leptin and LEPR play a key role in body weight and energy homeostasis. LEPR mutations are rare, autosomal recessive and result in hyperphagia and early onset monogenic obesity. Until now, the number of reported LEPR gene mutations is less than 60. The mutation detected in case 1 [(C.946C> A (p.P316T))] was previously reported in the literature. The mutation detected in case 2 [c.1220-1221insT] was shown for the first time in our patient. In conclusion, we think that monogenic obesity should be kept in mind and genetic studies should be done in patients with early onset severe obesity, hyperphagia and history of consanguinity.

P3-125**Fasting C-Peptide: A useful tool for diagnosis of Type II Diabetes Mellitus in overweight / obese adolescents living in a poor resources setting**

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Case Report: Two cases of type 2 diabetes mellitus (among which 1 case of metabolic syndrome) previously taken as type 1 diabetes mellitus in adolescents are presented and the evaluation and management are discussed. There was a family history of Diabetes mellitus in one of the adolescent. Both of them had signs of insulin resistance, they were overweight and obese respectively, poorly controlled on premix insulin. The laboratory test revealed a high HbA1C, dyslipidemia and high blood pressure (in one of them). The fasting C-peptide was within the normal range. The management plan consisted on lifestyle modification and medications made of metformin and intermediate acting insulin at 0.3UI/kg/day. 3 months after starting the treatment, we noticed a decrease of HbA1C, reduction of weight and blood pressure, and the improvement of the blood glucose. From these 2 cases, if they were T1 DM patients despite their weight, we should have expected to have a low fasting C-peptide. Both patients had acanthosis nigricans and metabolic syndrome in one of them but the C-peptide was within the normal range, meaning that their pancreas still secreting insulin, but it doesn't work properly because of resistance.

In conclusion, in the presence of signs of insulin resistance and obesity in a supposed T1DM patient, the fasting C-peptide can be useful to make the diagnosis of T2DM more probable. The management of this condition consists on lifestyle changes and medication (insulin and metformin).

Keywords: Type 1 diabetes mellitus, Type II Diabetes Mellitus, insulin resistance, metabolic syndrome, dyslipidemia, self-monitoring blood glucose, Fasting C-Peptide.

P3-126**Metabolic risk assessment in obese children using Hypertriglyceridemic waist (HTGW) phenotype. Can it be a useful screening marker?**

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Background: The prevalence of childhood obesity is dramatically increasing worldwide. Overweight and obesity are well known risk factors for metabolic disorders such as Insulin Resistance, Type II Diabetes, Arterial Hypertension and Non Alcoholic Fatty Liver Disease (NAFLD).

Aims: This study was conducted to assess the prevalence of Hypertriglyceridemic Waist phenotype (HTGW) among overweight and obese Greek children. Furthermore, to investigate whether HTGW phenotype could be used as a screening marker to detect children in risk of Insulin Resistance, Hypertension and NAFLD.

Methods: Data from 172 children (83 males) with mean age 9.7 years (SD=2.5 years) were analyzed. Triglycerides-Glucose (TyG) and Homeostasis Model Assessment for insulin resistance (HOMA-IR) indices were used as predictors of insulin resistance. TyG index was calculated as $\ln [triglycerides\ (mg/dl) \times \text{fasting}\ glucose\ (mg/dl)/2]$. HTGW phenotype was defined as Waist Circumference (WC) \geq 90th CDC percentile and triglyceride levels \geq 100 mg/dl for children 0 to 9 years of age and \geq 130 mg/dl for 10 to 19 years old. Elevated arterial pressure was defined as Systolic Arterial Pressure (SAP) or Diastolic Arterial Pressure (DAP) \geq 90th percentile. Alanine aminotransferase (ALT) \geq 25.8 U/L (boys) and 22.1 U/L (girls), was defined as abnormal. Chi-square tests were used for the comparison of proportions and Student's t-tests for the comparison of means.

Results: 43.2% of the children had waist circumference above the 90th percentile and 20.9% had elevated triglycerides. HTGW was present at 16.3% of the sample. No gender or age differences were found among children with HTGW. Significantly lower levels of HDL were found in cases with HTGW ($p<0.001$). WHtR ratio was significantly greater in cases with HTGW ($p=0.007$). Mean TyG was 8.79 (SD=0.32) for those with HTGW and 8.0 (SD=0.37) for those without HTGW ($p<0.001$), while subjects with HOMA-IR \geq 2.5 had a greater proportion of HTGW (23.4% vs. 8.8%, $p=0.030$). SAP and DAP did not differ in the presence of HTGW, while subjects with and without elevated blood pressure were not different in the presence of HTGW ($p=0.596$). NAFLD risk was not found to be associated with the presence of HTGW ($p=0.316$).

Conclusions: High prevalence of HTGW phenotype was detected among overweight and obese children and it was significantly and positively correlated with insulin resistance and lower HDL levels. Therefore, it could be a useful and cost effective marker for early detection of children in risk of developing metabolic disorders.

P3-127**Rosuvastatin therapy in children with heterozygous familial hypercholesterolemia, efficacy, and security of low régimen of therapy**

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Introduction: Heterozygous familial hypercholesterolemia is as frequent as 1: 200-500, and the mortality risk is four times more than unaffected children. Nutritional therapy in addition to physical activity can help but is not enough to avoid later morbidity and mortality. Studies have shown efficacy in children, but we do not have enough data for long term safety.

Aim: to compare two regimens of therapy using rosuvastatin 10 mg ; once daily and the other once every other day. observation period was 6 months.

Methods: 46 children with ages between 10- 15 years, without obesity or other hormonal diseases, were assigned randomly to one of two groups;

Group 1 : 10 mg / daily

Group 2 10 mg every other day

Basal lipids were registered and every three months twice during the study

Nutritional recommendations and physical activity were given to both groups.

Results: 23 children were included in each group. basal lipid levels were comparable in both groups before therapy. Group 1 with daily therapy showed decrease of CT And LDL more than the group 2 but not Statistically significant. No one shows elevated liver enzymes or muscle pain. Values are reported en mg/dl.

Conclusions: Rosuvastatin therapy every other day can be of comparable efficacy as daily therapy in management of elevated cholesterol levels in children . Being a lifelong therapy, every other day regimen can be used with equal efficacy and probably with minor side effects in children.

Table 1. Values of basal lipids and of each group after therapy

	Total Cholesterol	LDL	HDL	TG
Basal	266	202	42	110
Group 1	150	83	51	81
Group 2	168	100	48	99

P3-128

Lipid and glucose profiles in obese Algerian children and adolescents

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Introduction: Obesity constitutes a risk factor for several early-onset metabolic disorders. The problem is escalating in Africa, where the number of obese or overweight children and adolescents has increased by almost 50% since 2000 according to World Health Organisation (WHO) data).

Objectives: To determine the lipid and glucose profiles in Algerian children adolescents with obesity, defined as body mass index (BMI) >97th centile according to WHO growth data 4≤10 years old, 1>10 years), but never reached the threshold of 126 mg/dl in our population. In Algerian children adolescents with obesity, defined as body mass index (BMI) >97th centile according to WHO growth data.

Patients and Methods: Retrospective study of obese subjects aged 5-19 years without known type 1 or 2 diabetes or previous systemic illness, followed in a single center over a 10-year period.

Auxological data were collected and compared against WHO reference information. Total cholesterol, high and low density lipoproteins (HDL and LDL), triglyceridemia and fasting plasma glucose (FPG) were measured.

Results: During the period of January 2007-December 2018, 231 patients (102F:129M) presented with obesity of whom 50 (28F:22M) were enrolled in the study. At initial assessment mean±SD age was

10.20±3.5 years, height 138±19 cm, BMI 2.95±0.90. Median (range) HDL cholesterol were 42 mg/dl (15-89) with low levels (<40 mg/dl) in 18 (36%) patients (6≤ 10 years, 12>10 years). Median (range) triglyceride levels were 100.5 mg/dl (35-187) with high values (≥150 mg/dl) observed in 12 (24%) patients (5 ≤10 years old, 7>10 years) (n=100 mg/l in 5 (10%) patients)

Conclusion: Hypo-HDL-cholesterolemia followed by hypertriglyceridemia are the most prevalent metabolic abnormalities in our study population, affecting up to a third of patients. While overt diabetes mellitus was not found, 10% of patients had impaired fasting glucose. To reduce the morbidity and mortality inherent to cardio-metabolic risk, it is essential to establish a national strategy to prevent and control obesity in Algerian children.

P3-129

Influence of anthropometric indices at birth on obesity characteristics in school-age children

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Influence of anthropometric indices at birth on obesity characteristics in school-age children Latyshev D. Yu., Lobanov Yu. F.? Latyshev O. Yu. *, Karkova T.A.

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Keywords: Obesity, children, body length, body mass index

Objective: To study the relationship between anthropometric data at birth and the course of obesity in school-age children.

Materials and Methods: A retrospective analysis of developmental histories of 28 (9 girls) full-term children aged 10 to 15 years with obesity (SDS BMI > 2.0), average age 12.2 ± 1.9 years, was carried out. Estimated body weight and body length at birth. Content of cholesterol, β-lipoproteins, high density lipoproteins (HDL), low density lipoproteins (LDL), triglycerides (TG), glucose. To assess the relationship of factors, the Pearson correlation coefficient (r) was used, the values 0 - 0, 29 - very weak; 0.3-0.699 - average; 0.7-1 - strong correlation.

Results: The average length at birth of children in the studied group was 55.0 ± 1.7 cm. An inverse correlation relationship was established between body length at birth and SDS BMI (r = - 0.395). Significant correlations between body length at birth and blood glucose level (r = - 0.070), triglycerides (r = - 0.050), HDL (r = - 0.204), LDL (r = - 0.204), systolic (r = 0.010) and diastolic (r = 0.070) pressure was not detected.

The average value of body mass index at birth was 3873.3 ± 481.8 grams. An inverse correlation was established between the mass at birth and carbohydrate metabolism indices: the level of triglycerides (r = - 0.441) and LDL (r = - 0.323). In addition, an inverse correlation was found between the birth weight by systolic (r = - 0.402) and diastolic (r = - 0.456) pressure. Significant correlation with other studied factors were not revealed findings.

The influence of the child's body length at birth on SDS BMI in children with obesity has been established: the shorter the body length at birth, the greater the value of the SDS BMI index in the development of obesity at school age.

The baby's mass at birth has an impact on fat metabolism and blood pressure; the lower the birth weight, the higher the level of systolic and diastolic pressure, triglycerides and LDL cholesterol in the development of obesity at school age.

P3-130

Acanthosis nigricans as a presentation of severe insulin resistance in obese children

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Acanthosis nigricans is a common skin presentation of insulin resistance. We may observe different forms of its severity. Pathogenesis of this disorder is correlated with an action of insulin to keratinocyte and dermal fibroblasts via interaction with IGFR1.

We'd like to present a medical history of two patients admitted to our clinic because of severe acanthosis nigricans. Boys were at the age of 13 and 14 years. We diagnosed carbohydrate metabolism disorders with severely increased levels of fasting insulin and excessive secretion of insulin in oral glucose tolerance tests. We excluded all potential reasons: malignancy and endocrine disorders responsible for acanthosis nigricans. We are still waiting for the results of genetic tests. After dietary intervention resulting in successful lost of weight we observed substantial decrease in insulin levels and crucial reduction of acanthosis nigricans.

Loss of weight is the most important factor leading to improvement of metabolic disorders presented in obese patients. Features of insulin resistance deplete more effectively in biochemical tests than in a phenotype of those patients.

Fetal, Neonatal Endocrinology and Metabolism (to Include Hypoglycaemia)

P3-131

Growth prognosis of Small for Gestational Age in Korea : Risk of early adolescence

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Purpose: Small for gestational age(SGA)babies at increased risk of growth retardation. This is very important issues for them but lacks attention. So we hope this study deserves better guidance.

The objectives of this paper is to illustrate the importance of this critical issues and to outline growth prognosis at the beginning of adolescence of female and male babies born small for gestational age(SGA) in comparision to controls born appropriate for gestational age(AGA). It is also a more detailed study of SGA infants in Korea.

Methods: This study is a case control descriptive study of children born small for gestational age in 2003-2006 at Daegu Medical Center, Daegu metropolitan city, Korea. The body weight, height, head circumference at birth have been retrieved from the medical records and the diagnosis of intra-uterine growth retardation(IUGR)have been made based on the growth curves published by Korean pediatric Association in 2017. The current height and weight are taken for the two groups and compared with each other using the 't test' for a better understanding of the prognosis of growth in children born SGA. Thirty cases and Thirty controls were recruited with neonatal infection and chromosomal abnormalities being the criteria of exclusion. The prevalence of children born SGA is 3 % in our study.

Maternal risk factors including smoking and eclampsia, diabetes were noted in both groups.

Results: The majority of children with intrauterine growth retardation(IUGR) catch similar growth to that of their controls. No adverse consequences are observed in these children at the age of 11-12years. No correlation observed between IUGR and current weight and height of the children except for the current weight of the girls born SGA which is less compared to that of the controls. None of those children born SGA needed a GH treatment for the achievement of their optimal growth.

Conclusions: Children born SGA have similar dimensions in early adolescence compared to those born with a size appropriate for Gestational Age (AGA) except for the weight of the girls born SGA. The awareness of medical personnels and parents for early referral to treatment with GH therapy if necessary.

P3-132

Recurrent apnea in a boy suffering from congenital hyperinsulinism in the course of diazoxide treatment

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Congenital hyperinsulinism (CHI) is rare disease which prevalence is estimated as 1:2500 to 1:50000 born newborns. Main reason of the disease are genetic mutations in genes responsible for regulation of insulin secretion. First line treatment is diazoxide therapy.

Our patient was diagnosed with CHI at the age of 2 months. Biochemical tests prooved diagnosis of CHI. He presented lack of negative feedback and secreted pathologic amount of insulin – during episode of hypoglycemia. We run diagnostic procedure to asses endocrine and metabolic systems which might be a reason of hypoglycemia. We denied diagnosis of inborn metabolic. We observe good response of counterregulatory hormones. At the beginning he was treated with diazoxide with good effects. Patient

achieved normalization of glycemas. Unfortunately when a dose of the drug was increased the patient started to present unexpected complications. In December 2017 he had first episode of apnea which were not connected with hypoglycaemia.

Patient run neurological, cardiological, gastroenterological assessment – none of abnormalities were found. Apnea's went away when we decreased dose of diazoxide. Since December 2017 the boy presented next 3 episodes of apneas not related with hypoglycemia, they always appeared when the dose of diazoxide was increased (from 3,9 mg/kg/day to 4,9 mg/kg/day). We decided to decrease of diazoxide and implicate some new diet recommendations. Unfortunately we didn't achieve good glycemic control, so we decided to increase morning dose of diazoxide. After three days another apnea occurred again.

Because of intolerance to diazoxide therapy we decided to change the way of his treatment, removed diazoxide and gave him octreotide in injection four times a day. At the beginning we observed very good reaction and good glycaemic control, after few days we observed tendencies to decreased glycaemia. Because of lack of good response to the sandostatin therapy by itself we decided to mix up to ways of the therapy – and nowadays he is treated with diazoxide in smaller doses (3,7 mg/kg) and octreotide given via personal insulin pump (5,7 mcg/kg). Recently he needs to take hydrocortisone as well because of adrenal cortex suppression caused by octreotide. Currently glycemas are well controlled and no apnea occurred again.

P3-133

Relations of O₂ Supplementation to Blood Serum Insulin-Like Growth Factor-I in the Not-Life-Threatened Human Newborn; Role of Oral-Enteral Caloric Intake Beyond Axillary Temperature

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Introduction: Human newborn(NWB) respiratory derangements may be concomitant to oral/enteral caloric intake (KOE) insufficiency. We evidenced a possible involvement of axillary temperature(TEMP) in relationships between preterm birth (PTB) and blood serum Insulin-like Growth Factor-I(IG1) in NWBs. Here we evaluate the TEMP-independent role of birth gestational age(GA) and KOE in relations of O₂ supplementation in respiratory gases(O₂S) to IG1 in the not-life-threatened NWB.

Methods: NWBs with any among total parenteral nutrition, parenteral nutrition other than dextrose, blood component transfusion, postnatal corticosteroid treatment, therapeutic hypothermia,

life-threatening disease, diabetes mellitus(DM), endocrine diagnosis out of DM, malformation, and mother with DM were excluded. Each of 78 included NWBs had complete data availability for 1) same-day records at one of the first 5 postnatal days(x), 5 days after x(y) and 10 days after x(z) of postnatal age(PNA, unit:day), TEMP(unit:°C), total caloric intake(K) and KOE(K, KOE, unit: kcal/kg body weight/24hrs), pulse oximetry(SpO₂, unit: %), O₂S, and IG1 RIA measurements(unit:uM/dl), and for 2) gender(SEX), GA(unit:complete week; range=28–42), GA<=36(preterm birth, n=46), BW(unit:g; range=1200–4150), BW<=10.th centile for GA(SGA). We calculated: 1) averages over x-y-z times (i.e., (x+y+z)/3) for TEMP(TEMPM; range=36.1–37.0), IG1(IG1M), K(KM), KOE(KOEM), and SpO₂(SpO₂M; range=87.3–100.0), and 2) percents of KOEM over KM (i.e., (KOEM through KM)x100), KOEM%KM; range=24.5–100.0). IG1M normal score according to van der Waerden(IG1M-NS) resulted near-normally distributed. Multiple Linear Regression(MLR) was used for analyses(MLR computations; male SEX, SGA, O₂S at x(O₂Sx), condition absent=0, condition present=1)(n; male SEX, 43; SGA, 20; O₂Sx, 22).

Results: Partial correlation coefficient (pcc) for partial correlation between O₂Sx and outcome IG1M-NS was significant in MLR models bearing, as predictors, 1) SEX, SGA, PNA, TEMPM, KM and O₂Sx (pcc, r₂: -.391, p=.001) or 2) SEX, SGA, PNA, TEMPM, KM, O₂Sx and SpO₂M (pcc, r₂: -.379, p=.001) but not 3) GA and/or KOEM%KM in addition to SEX, SGA, PNA, TEMPM, KM and O₂Sx or 4) GA and/or KOEM%KM in addition to SEX, SGA, PNA, TEMPM, KM, O₂Sx and SpO₂M (MLR R₂:.351-.550, always significant).

Conclusions: Factors related to GA and/or to KOEM%KM may be related to O₂Sx - IG1M-NS relations after control for TEMPM in addition to SEX, SGA, PNA, TEMPM, KM, and SpO₂M.

P3-134

Persistent Hypoglycemia in Children: Hyperinsulinemia

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Congenital hyperinsulinemia occurs due to inappropriate insulin secretion from beta cells of the pancreas. It is the most common cause of resistant and recurrent hypoglycemia in neonates and infants and the treatment is very difficult. Although the incidence is reported as 1/50000, it is seen more frequently in consanguineous countries. Patients may present with lethargy, nourishment, irritability and seizures. If it is not treated, severe hypoglycemia may result in severe neurological damage. High glucose requirement in the diagnosis of congenital hyperinsulinism, detectable insulin level and ketone negativity are the key findings during hypoglycemia. Approximately 45-55% of the patients have an underlying genetic etiology. The most common mutations are ABCC8, KCNJ11, GLUD1 HADH, GCK, SLC16A1 hepatocyte nuclear factor 4 alpha and 1 alpha. In the treatment of drugs such

as diazoxide, octreotide, nifedipine may be used, while some patients may require surgical treatment.

Here, the aim of this study was to evaluate the clinical, genetic and therapeutic responses of hyperinsulinemia patients.

Cases: 8 cases of hyperinsulinemia diagnosed and followed in our clinic were evaluated. The age of the patients, their causes, treatment responses, genetic etiology were evaluated. Seven of the patients were diagnosed during neonatal and early infancy. In most of the neonatal cases presented with feeding problems and one of the patient presented with convulsion. In the case of a late diagnosis, the reason for the investigation was the low blood glucose level detected in the routine biochemical evaluation. The patient had motor and mental retardation at the time of diagnosis and it was learned that he was being followed up for autism. Three of the cases were siblings and there were 1 sibling death in the family. He died of multiorgan insufficiency during hospitalization. Most of the patients had a birth weight over 4000 grams.

Three patients received pancreatectomy because of inadequate response to medical treatment. Two patients received additional medical therapies besides diazoxide. In one patient, pulmonary hypertension secondary to diazoxide developed and treatment was replaced with octreotide. Pulmonary hypertension regressed after discontinuation of treatment.

Result: Hyperinsulinemia is more common in countries such as our country where the rate of consanguineous marriage is high. Early detection and treatment of hypoglycemia is very important for the prevention of neurological sequelae. Here, we wanted to draw attention to this group of diseases that are quite difficult to manage.

P3-135

Abstract withdrawn

P3-136

Abstract withdrawn

P3-137

Case report: A neonate with prolonged hypoglycemia

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Background: Transient hyperinsulinism (HI) is a condition characterized by high insulin level, low FFA level in a context of severe hypoglycemia in neonate. Our objective is to present a case of a transient hypoglycemia in a newborn. Evaluation and management of this condition is discussed.

Case Presentation: A 14 days old term baby was diagnosed with bilateral bronchopneumonia. He received antibiotics and nasal drop. On day 7, when the baby was about to be discharged, he developed respiratory distress, hypotonia, cyanosis and the mother claimed the baby was not sucking well since morning. The checked BG level (finger prick) was 20 mg/dl. We thought about hypoglycemic episode secondary to insufficient food intake. During 48 hours, hypoglycemic episodes continued despite increased GIR and boluses with 10% dextrose and full feeds via nasogastric tube. Hence, he was diagnosed as a case of prolonged hypoglycemia. BG was maintained on GIR of 7.9 mg/kg/min. Serum insulin level was high 7.9 μU/ml (>2μU/ml) with corresponding BG of 28 mg/dl, low FFA 0,233 mmol/l (<1,5mmol/l), negative urine ketones, good response of the GH, C-peptide and cortisol were not done because of financial issues. We would have expected to have a low insulin and high FFA levels in a context of hypoglycemia but we got the contrary. We concluded that it is a case of transient neonatal HI.

Conclusion: We believe that our patient had a transient hypoglycemia secondary to transient HI. His blood sugars were under control with the help of increased continuous infusion of glucose, 10% dextrose boluses and feedings.

HI is defined as persistent hypoglycaemia despite glucose requirement >8mg/Kg/min. It is the most common cause of transient and permanent disorders of hypoglycemia. The causes of transient HI are mostly found in IDM, IUGR, perinatal asphyxia, sepsis. Genetic disorders are more present in persistent HI. Blood sample (**critical sample**) to detect insulin levels should be drawn at the time of low BG. The diagnosis is made on this findings: Hyperinsulinemia (plasma insulin >2μU/ml), Hypofattyacidemia (p.FFA <1,5mmol/l), hypoketonemia (BOHB <2mmol/l), inappropriate glycemic response to glucagon 1mg (rise >40mg/dl), increased of GH and cortisol levels in response to hypoglycemia. High glucose requirement may support the diagnosis particularly when an insulin level is not available.

Signs of hypoglycemia are neither sensitive nor specific. Any baby that is unwell or who has signs that cannot be readily explained should have their BGL checked. Always look for the etiology of hypoglycemia and treat it.

Keywords: Neonatal Hypoglycemia, Hyperinsulinism (HI), Free Fatty Acid(FFA). IDM, IUGR

GH and IGFs

P3-138

Factors affecting Growth Response to Growth

Hormone (GH) therapy in children with short stature and normal GH and IGF-I secretion and no bone age delay

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Background : There are inconsistencies in the results reported in a small number of previous studies into growth hormone (GH) treatment of short children with idiopathic short stature (ISS).

Patients and Methods: Our study included 20 prepubertal (Tanner 1) or peri-pubertal (Tanner 2) children with short stature (HtSDS < -2) and/or HtSDS > 1SD below their mid parental height SD (MPHtSDS), slow Growth velocity(< -1), with normal Peak GH to provocation (15.58 +/- 6.95 ng/dl), normal IGF-1 SDS (-0.9 +/- 0.6), Tanner 1 (n = 15, Tanner 2 = 3, Tanner 3 = 2) and no bone age delay. We treated all the children for 2.5 +/- 1.5 years with rhGH 0.4 mg/kg/day and assessed their linear growth at the end of this period in relation to different possible modifying factors.

Results: Our children on GH therapy increased their HtSDS by 0.77 +/- 0.5 at the end of the treatment period (2.5 +/- 1.5 years). The effects of different factors on their growth response are summarized in table.

Discussion: Children below 9 years with HtSDS < -2.5 and those whose HtSDS was 1SD or more below MPHtSDS grew better on GH therapy compared to older children and those with HtSDS > -2.5 and were less than 1SD from their MPHtSDS.

Conclusion: Growth response to GH therapy in short children with normal GH-IGF-I axis, appears to be significantly better in those younger than 9 years, with HtSDS < -2.5 for the population and with HtSDS > 1SD below their MPHtSDS.

P3-139

Responses to growth hormone (GH) therapy in children with short stature with normal GH secretion and slow growth velocity

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Background: Variability still exist about the growth response to growth hormone (GH) therapy in children with idiopathic short stature.

We describe the growth response to GH therapy (0.05 mg/kg/ day) for > 2 years in 20 prepubertal children with idiopathic short stature (ISS) who had slow growth velocity (< -1 SD), normal GH response to provocation and who were significantly shorter than their mid-parents height SDS MPHtSDS (-1 difference).

Results: The height SDS gain in a mean of 2.5 years = 0.77 SD, with a significant increase in IGF-I (triple) and normal progression of puberty. The difference between children HtSDS and MPHtSDS changed significant from -1.1 +/- 3 at the beginning of GH therapy to -0.3 +/- 0.5 at the last visit. Table 1.

	HtSDS – MPHtSDS before GH Therapy	HtSDS – MPHtSDS after GH therapy	HtSDS gain after GH therapy
Ht SDS < -2.5	-1.20	-0.20*#	0.98#
HtSDS > -2.5 <-2	-0.93	-0.32*	0.60
More than 1SD below their MPHtSDS before GH therapy	-1.5	-0.57*#	0.88#
Less than 1SD below their MPHtSDS before GH therapy	-0.71	-0.1*	0.62
IGF-I increment > 150%	-1.2	-0.4*	0.7
IGF-I increment < 150%	-1.1	-0.25*	0.83
GH response > 15 ng/dl	-1.13	-0.29*	0.8
GH response < 15 ng/dl	-1.07	-0.37*	0.69
Stayed prepubertal during therapy	-1.34	-0.27*	0.71
Proceeded to Tanner 3 & 4 during therapy	-1.36	-0.37*	0.78
Age < 9 years at the start of GH	-1.2	-0.1*#	1.1#
Age > 9 years at the start of GH	-1.04	-0.45*	0.58

*=p<0.05 before vs after therapy, #= p < 0.05 comparing different groups

The HtSDS gain was correlated with the duration of GH therapy ($r = 0.82$, $p < 0.0001$), negatively with age at the start of treatment ($r = -0.544$, $p = 0.01$, and negatively with the bone age delay in years ($r = 0.44$, $p = 0.04$). No correlation between HtSDS gain and IGF-1, Peak GH to provocation, or change in IGF-I ($r = 0.09$, -0.18 , and -0.02 respectively).

Conclusion: We report significant gain in HtSDS in prepubertal children with ISS on GH therapy. Better response was achieved with prolonged duration of GH therapy, younger age and delayed bone age at the beginning of therapy.

		Start of treatment	On last visit	Differences
Age years	Mean SD	9.88 2.62	12.36* 2.27	2.49 1.61
IGF-I units	Mean SD	143.4 57.4	407.1* 162.4	263.7 105
HtSDS	Mean SD	-2.34 0.41	-1.57* 0.55	0.77 0.14
Pubertal stage	Mean SD	1.35 0.65	2.7* 1.35	1.35 0.7

P3-140

Assessment of body composition of Children with short stature on growth hormone therapy and its relation to serum IGF-1

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Background: Isolated Growth Hormone Deficiency (IGHD) is a common endocrinological cause of pediatric short stature. Growth hormone produces most of its actions via insulin-like growth factor 1 (IGF-1) which is affected in IGHD. GH can affect body composition via its action on body metabolism.

Objectives: This study aimed to prospectively assess body composition among IGHD group starting GH replacement and after six months of therapy versus control group and its relation to serum IGF-1.

Subjects and Methods: forty IGHD subjects (22 males and 18 females) with age mean 11.34 ± 4.03 . Auxological anthropometry and biochemical changes including height standard deviation score (HT-SDS), predicted adult height (PAH), age of growth velocity peak ("AGVP"), body mass index (BMI), bone age (BA), (IGF-1) and body composition were compared to control group ($n=40$) at start of growth hormone therapy and after six months.

Results: After six months of GH therapy, there was significant change in body composition with significant increase in free fat mass (FFM), muscle mass (MM) in relation to the increased level of serum IGF-1. While there was significant decrease in BMI, fat mass (FM) compared to control group. There was significant increase in HT-SDS, PAH, AGVP, with no significant increase in bone age compared to control group.

Conclusion: After six months of GH therapy for IGHD children, GH has its effect on body composition mainly muscle mass rather than fat mass with the significant increase of IGF-1 level, PAH and AGVP. Six month of therapy was not significant duration to produce changes on bone age.

P3-141

Treatment Outcome of Growth Hormone in Turner Syndrome Children

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Background: Turner syndrome (TS) patients frequently have short stature. Females adults with TS are usually 20 cm shorter than normal females. Growth hormone (GH) can improve final height in TS patients.

Objective: To evaluate GH therapy for children with Turner syndrome in term of efficacy and side effect

Patient and method: This serial cases study was done in TS patients in a period August 2018 to April 2019. Patients were enrolled if they had at least 1 year of GH treatment. The patients were diagnosed and treated in Vietnam National Children's Hospital. GH was indicated in TS patients when height was less than $-2SD$ according to WHO 2007. The starting dose of GH was 0.05 mg/kg/day.

Results: In our study 49 TS patients were enrolled: 19 patients with 45,X (38.8%); 15 TS patients with mosaics (30.6%); 15 patients with structural abnormalities (30.6). Mean age at study time was 8.2 ± 3.5 (Min = 1; Max = 15). Patients' height before treatment was 110.5 ± 15.5 cm. Patients' height 1 year, 2 year, 3 year, 4 year after GH treatment were 117.5 ± 14.9 cm; 119.9 ± 24.9 cm; 127.8 ± 13.8 cm; 130.2 ± 13.9 cm, respectively.

In patients aged < 5 years, height SD score was $(-2.98) \pm (-1.87)$ before GH treatment ($n=9$); $(-2.33) \pm (-1.77)$ 1 year after treatment ($n=9$); $(-2.00) \pm (-1.66)$ 2 years after treatment ($n=6$); $(-1.53) \pm (-0.78)$ 3 years after treatment ($n=4$).

In patients aged from 5 to < 10 years, height SD score was $(-3.44) \pm (-2.13)$ before GH treatment ($n=20$); $(3.02) \pm (-1.98)$ 1 year after treatment ($n=19$); $(-2.22) \pm (-1.30)$ 2 years after treatment ($n=7$); $(-2.78) \pm (-1.00)$ 3 years after treatment ($n=4$).

In patients aged from 10 to 15 years, height SD score was $(-2.67) \pm (-2.00)$ before GH treatment ($n=20$); $(-2.58) \pm (-1.73)$ 1 year after treatment ($n=20$); $(-2.00) \pm (-0.67)$ 2 years after treatment ($n=12$); $(-1.89) \pm (-1.11)$ 3 years after treatment ($n=6$).

In term of side effect, 12.2% patients had headache during treatment; 2% patients had arthralgia. These side effect were mild and transient.

Conclusion: GH treatment was effective in increasing height SD score in TS patients.

P3-142**Pituitary imaging in 23 children with growth hormone deficiency**

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Introduction: Growth hormone deficiency (GHD) is a non-exceptional cause of short stature. Hormonal evaluation and hypothalamic-pituitary MRI are essential to establish the etiological diagnosis. The objective of our study is to assess the different pituitary lesions found in imaging in a group of children with GHD.

Patients and Methods: This is a retrospective longitudinal study of 23 cases of GHD who underwent pituitary MRI examination collected in the Endocrinology-Diabetology Department of Mohammed VI University Hospital.

Results: The mean age at diagnosis was 10,9 years with a sex ratio (M/F) of 2.14. Mean height Z-score at time of diagnosis was -4,46 SD. The mean bone age (BA) at the time of diagnosis was 6,23 years. The delay of BA over the chronological age was of 5,37 years on average. The diagnosis of total GHD was found in 77,3% of patients and partial GHD in 22,7% of patients. The isolated deficiency was noted in 31,8% of cases and multiple deficiencies in 68,2 % of cases. Magnetic resonance imaging of the hypothalamic-pituitary region was normal in 27,3% of cases. Pituitary stalk interruption was observed in 56,5 % of patients, pituitary hypoplasia was observed in 17,3 % of patients, an empty sella was observed in 12 % of patients, and agenesis of anterior pituitary in 12% of patients.

Most of the children with MPHD showed pituitary stalk interruption in 43.75% of children and anterior pituitary aplasia/hypoplasia in 25% of children, while only (18.75%) children with MPHD had normal MRI.

Conclusion: The multiplanar capability of MR imaging plays an important role in the assessment of the hypothalamic-pituitary area and in determining the underlying cause of various pituitary disorders in GHD. And it has been shown that the prevalence of pituitary abnormalities is in most cases greater in patients with combined GH deficiency than those with an isolated GH deficiency.

P3-143**The convulsions Maze: Epilepsy versus Hypoglycemia**

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Introduction: Diagnosing a seizure can be tricky. The first thing a doctor should do is to rule out other conditions, such as non-epileptic seizures. One of these conditions may be metabolic disturbance as hypoglycemia. Growth hormone deficiency is commonly presented with short stature during childhood .hypoglycemia is a rare presentation of the disease.

Case Report: a four year and seven months male child, diagnosed as a case of epilepsy due to focal convulsions since the age of 2 years and was on antiepileptic drugs being uncontrolled so

parents sought another medical advice where the occurrence of hypoglycemic attacks were identified and doctors thought about being a case of inborn error of metabolism and investigations were done. He presented to us by loss of consciousness and very low random blood glucose level was detected, a golden sample of hypoglycemia was withdrawn which revealed a picture of growth hormone deficiency. MRI brain was performed showing hypo-plastic pituitary gland. By starting growth hormone replacement therapy the seizures attacks stopped.

Conclusion: random blood sugar is crucial in any case presented with convulsion as a first step. Golden sample is mandatory in such situations .growth hormone deficiency may presented with hypoglycemia which is quite rare.

P3-144**A case of paediatric GH-secreting pituitary adenoma apoplexy**

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Background: Paediatric pituitary adenomas comprise rare but challenging pathologies in children and adolescents related to their endocrine and neurological characteristics.

Objective and Hypotheses: We aimed to describe a case report of growth hormone (GH)-secreting pituitary adenoma apoplexy.

Method: a 11-year-old girl presented with fever, sudden headache with vomiting. She abruptly developed bilateral hemianopia. On suspicion of infectious meningitis, lumbar puncture and brain MRI were performed on admission.

Results: The physical exam was normal, without neurological abnormalities except for visual disturbances. Auxological parameters were above 95th percentile (height 2.25 SDS, weight 1.85 SDS). Biochemistry laboratory and cerebrospinal fluid analysis were normal. Brain MRI showed a 33 mm-sellar and suprasellar mass with pituitary stalk and optic chiasm dislocation and third ventricle compression; it has heterogeneous signal features and contrast enhancement, highly suggestive of hemorrhagic transformation of a pre-existing pituitary adenoma. The endocrine investigations demonstrated central hypothyroidism, hypocortisolism, GH deficiency and diabetes insipidus. The lesion was surgically removed with a transphenoidal approach. The histological examination and immunohistochemical staining were compatible with somatotroph GH-secreting adenomas diffuse necrosis and hemorrhage areas. In the postoperative period, multiple pituitary hormone replacement therapy (hydrocortisone, desmopressin, estrogen and L-thyroxine) was started with good response. GH substitution was started 7 months later.

Conclusion: Pituitary apoplexy in children and adolescents is a rare entity that requires rapid and adequate treatment to prevent a life-threatening situation. Pituitary failure may develop with the effect of adenoma itself or following surgical excision. Clinical and laboratory signals may be suggestive and MRI neuroimaging is fundamental for diagnosis.

P3-145**Final adult height of children with idiopathic short stature: a multicenter study on GH therapy alone started during peripuberty**

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Purpose: To evaluate the efficacy of GH in improving FAH in ISS children in a multicenter study.

Methods: A real-world observation was carried out. Children with ISS in seven hospitals in China were enrolled. The height gain standard deviation score and the height gain over the target height were evaluated.

Results: There were 344 ISS patients (217 boys and 127 girls). The baseline average age of boys and girls was 12.7 and 11.7 years, with bone age of 11.7 and 10.1 years, respectively. The baseline height SDS of boys and girls was -3.07 and -2.74, and the FAH SDS was -1.91 and -1.38, respectively. Compared with the baseline height SDS, the FAH SDS was significantly increased in both boys and girls (both P=0.0000). The FAH SDS was the highest (gain by 1.54 SD) in the ≥2y treatment course group. 218 patients (218/344, 63.4%) had an FAH SDS > -2 SD. Among these patients, girls in the 1-2y treatment course group and ≥2y group had a FAH SDS higher than TH SDS. A multivariate linear regression model was used to analyze the results, with FAH SDS as the dependent variable. It was found that the treatment course and baseline height SDS in the boys' model were statistically significant (P<0.05), whereas the baseline height SDS and baseline bone age significantly affected the girls' FAH SDS (P<0.05).

Conclusions: When GH is applied for treating ISS, a treatment course of 2 years or more can achieve better efficacy.

P3-146**Growth hormone deficiency after radiation therapy for brain tumor how to manage?**

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Introduction: Radiation induced growth hormone deficiency (GHD) is one of several important factors in the aetiology of short stature complicating the treatment of brain tumours in childhood.

If such a child is clinically well, shows a poor growth rate and biochemical evidence of GH deficiency, then a 1 year trial of GH is justified.

The aim of this study is to evaluate growth and assessed Pituitary function (GH deficiency) in children who received cranial irradiation for brain tumours.

Materials and Methods: Thirteen children were studied : 10 boys and 03 girls with sex ratio of 3 boy for 1 girl with age rang from 08 years to 17 years.

Results: The Neoplasms listed are: 03 medulloblastomas, 02 Germinomas, 02 astrocytomas, two ependymomas, 01 craniopharyngioma, 01 pineoblastoma, 01 retinoblastoma, and (01) tumor of the cavum. The stature is found delayed <-2DS for 08 children, the 05 others children showed no delay in their stature. A hormonal exploration, IGF1 levels were low in 08 cases and normal in 05 cases, stimulation tests of GH performed in 07 cases (one patient was lost to) returned for a complete deficiency in GH in 06 cases and partial for one patient. Except for the 02 patients with persistence of the neoplastic process, the rest of the patients had a sequellar neoplastic status, which allowed treatment with GH in 05 cases with no incident during GH treatment, all children so treated showed an increase in height. However, after 02 years following the end of the GH a recurrence is noted in one case.

Conclusion: We conclude that GH deficiency are common after cranial irradiation for brain tumors. Linear growth appears to reflect GH status accurately in children with brain tumors. Our findings reflect the need for prospective growth monitoring of children with brain tumors treated with cranial irradiation.

P3-147**Vitamin D status in patients with short stature**

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Introduction: The relationship between the level of vitamin D and the IGF1 is complex. A normal level of vitamin D is necessary for good bone growth. On the other hand, the normal growth process is affected by the excess or the deficit of growth hormone. Thus, the main purpose of our work is to demonstrate the particularity of the vitamin D status of patients with growth hormone deficiency compared to other causes of short stature.

Methods: This prospective study was carried out in the Department of Endocrinology and Metabolic Diseases at the Mohammed VI University Hospital, Oujda, Morocco. Over a period of 5 years, 62 patients with short stature were included. The level of Vitamin D was measured as part of the 1st intention assessment for each patient.

Results: The average of the age was 11 ± 5 years with a mean diagnosis age of 6 years. The sex ratio was 1.13 including 53% of girls. The average birth weight was 3034 grams. Patients presented a statural delay at -3.5 DS moving from -1.5 DS to -7 DS, they were also underweight at -2.5 DS.

Vitamin D deficiency was observed in 85% of patients. The mean of IGF1 of those patients was 120.5 ± 90 ng/l. The mean of vitamin D level in patients with growth hormone deficiency (32%

of all cases) was 21.4 ± 8.6 ng/ml with no significant correlation comparing with the mean of vitamin D level in patients with other causes of their short stature such: syndromic statural delay, chronic diseases, low birth weight, pubertal delay and constitutional bone diseases. These patients have a mean vitamin D level of $20.4 \text{ ng/ml} \pm 8.6$ (p de 0.69).

Discussion: Growth hormone and IGF1 deficiency have skeletal and metabolic consequences. Vitamin D deficiency maintains these serious effects on growth. The tight relationship between vitamin D levels and IGF1 makes correction of vitamin D necessary to have an optimal statural growth.

P3-148

Short stature in children in the Department of Endocrinology in the east of Morocco

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Introduction: Statural delay is a common reason for consultation in Endocrinology. It is defined as a length less than 2 DS or a slowdown in growth rate. Etiological research involves anamnestic and clinical data. The biological and radiological explorations permitted to select a primary or secondary etiology taking into account the frequency of idiopathic stature delay. The aim of our work is to analyze the clinical, etiological and evolutionary profile of stature and weight delay in patients admitted in our Department to explore a short stature.

Methods: This prospective study was carried out in the Department of Endocrinology and Metabolic Diseases at the Mohammed VI University Hospital, Oujda, Morocco. Over a period of 5 years, 162 patients were included in the study. These patients were admitted in our Department for a short stature.

Results: The average of the age was 11 ± 0.5 years with a mean diagnosis age of 6 years. The sex ratio was 1.25 including 55% of boys. The average birth weight was 3034 grams. Patients presented a statural delay at -3.5 DS moving from -1.5 DS to -7 DS, they were also underweight at -2.5 DS.

The stimulation test was carried out in 52% of patients, the coupled propranolol-Glucagen test was the most used test (62% of cases). The short stature secondary to growth hormone deficiency was retained in 28% of patients. The etiological profile was dominated by idiopathic delay observed in 32% of patients followed by the growth hormone deficiency in 28% of cases. The other causes of the short stature in our population were: syndromic stature retardation, chronic diseases, low birth weight, pubertal retardation, and constitutional bone diseases. Eighty percent of patients were treated with recombinant growth hormone. The average growth rate was 9 centimeters during the first year of treatment.

Discussion: Exploration of short stature is essential even in view of the frequency of idiopathic delay. Therapeutic management involves the treatment of causal disease and recombinant growth hormone for patients with growth hormone deficiency.

P3-149

Local Lipoatrophy following Recombinant Human Growth Hormone Administration in Prader Willi Syndrome

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Background: Recombinant human growth hormone (rhGH) is usually administered via subcutaneous injections. Besides well-known adverse events such as peripheral edema, benign intracranial hypertension, and slipped capital femoral epiphysis, a less known and rare side effect is local lipoatrophy, a phenomenon with an incompletely understood pathophysiology. Here, we report a case of Prader Willi Syndrome (PWS) who presented with local lipoatrophy following hGH.

Case: A 3.5 year old boy was admitted with newly diagnosed PWS. On admission, weight was 17 kg (0.5 SDS), height was 96 (-1.1 SDS), and body mass index (BMI) was 18.5 (2 SDS). rhGH therapy was started at the age of 3.5 years (initial dosage 0.015mg/kg/day, final dosage 0.035mg/kg/day) after his admission. His last BMI was 16.5 (0.6 SDS) with an improvement. Although, no high dosage of rhGH was used, lipoatrophy in both arms was observed at the 2. year of rhGH therapy. No any side effects of rhGH was observed during the follow-up.

Conclusion: Severe local lipoatrophy in injection sites of extremities has only described in a few reports. The present case details a rare side effect of rhGH in genetically proven PWS on an optimal dosage of therapy. Lipoatrophy can be another side effect of rhGH therapy independent from dosage. Moreover, complexities of biosimilar agents in their production, or clinical application have raised questions among experts and some side effects can be occurred by biosimilar agents. Further accumulation of genetically proven PWS cases and long-term treatment outcomes of both original molecule and biosimilar agents are required to understand the dynamics of rhGH especially in PWS.

P3-150

Features of somatropin replacement therapy in a patient with Floating Harbor Syndrome

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Background: Growth hormone (GH) deficiency in children, confirmed by stimulation diagnostic tests, in some cases is accompanied by low effectiveness of somatropin replacement therapy, which may be associated with rare genetic syndromes.

Aim: To study the growth effects of GH therapy in treating a patient with Floating-Harbor Syndrome

Methods: A GH deficiency was diagnosed in a patient 3 years old using clonidine test (peak stimulated GH 7,2 ng/ml). The patient was observed by a neurologist, cardiologist, ophthalmologist with diagnoses: organic brain disease perinatal genesis, stigma dis-embriogenesis, delayed speech development, open oval window, convergent paretic squint.

MRI of the brain and pituitary showed no pathology. Deficiency of other hormones of the adenohypophysis wasn't detected. The bone age significantly lagged behind the passport, was 8-9 months.

GH replacement therapy was prescribed at the age of 4,5 years. SDS growth at the time of observation $-2,38 \pm 0,86$ ($-4.09 \div -1.2$). Growth rate $4,8 \pm 2,68$ cm/year ($0,5 \div 10$ cm). SDS growth rate $0,4 \pm 2,07$ ($-4,3 \div -2,55$).

Results: During the molecular genetic survey for the diagnosis of mutations in the genes responsible for the development and functioning of the pituitary-GH-IGF-I system, no mutations were identified. Additional examination revealed mutations in the SCRAPc7466C>G gene, which made it possible to diagnose the presence of Floating Harbor syndrome.

Conclusions: Diagnosis of GH-deficiency, based only on the determination of GH by stimulation tests, does not allow to verify the pathogenetic diagnosis. Additional carrying out molecular genetic diagnostics in difficult cases while observing a patient over time at low (or insufficiently high) growth rates during treatment with somatropin is necessary to predict treatment.

development and micropenis(stretched penile length of 2.1cm) at age of one. His gross without support at 10 months of age and walking alone at 24 months of age), while language development was severely retarded (only a few words spoken at 5.5 years of age). At age of one year, he showed proportionate short stature with a length of 67 cm [<-2 SD], a weight of 6.7 kg(<-2 SD). He had dysmorphic facial features: a triangularly-shaped face, deep-set eyes, long eyelashes, lowest malformed ears (hypoplastic helix, small ear lobe), a long nose with narrow bridge, a short philtrum, thin lips, microdontia and malocclusion. Karyotype was 46XY, Cerebral MRI showed a very thin pituitary stalk, an absent posterior pituitary. He developed mental retardation and attended an unusual elementary school at 6.5yrs. From 4.83 years old, he was treated with growth hormone (GH) (0.37mg/kg/week) for the indication of short stature born small for gestational age. During the 51 months' GH treatment(0.37~0.46 mg/kg/week) with the 80% adherence, his height SD increased from -4.1 SD to -2.57 SD, indicating partial GH's growth promoting effect on large SGA dose. The bone age was 4 years delay at age of 9 years at last follow-up. At age of 7, We performed targeted exome sequencing, considering several syndromes with similar phenotypes. An identified variant was confirmed by Sanger sequencing of the patient and his parents. Finally, the patient was confirmed as the FHS with a novel SRCAP mutation[Exon34: c.7245_7246delAT; p.(Ser2416fs)], which is a frameshift mutation resulting in early termination of the protein; it was not found in either of his healthy parents or a control population.

Conclusion: We present a boy with FHS with a novel SRCAP mutation. Our data imply that GH therapy exerted partial effect on the growth.

Growth and Syndromes (to Include Turner Syndrome)

P3-151

Long-term follow-up study for a boy with Floating–Harbor syndrome due to a de novo novel heterozygous SRCAP mutation

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Background: Floating-Harbor syndrome(FHS) is a rare autosomal dominant genetic disorder associated with heterozygous mutations in SRCAP gene. The SRCAP protein activates the cAMP-response element binding protein-binding protein(CREBBP) gene that is involved in the regulation of cell growth and division.

Objective: To report on long-term follow-up data of a boy with FHS

Methods: We perform targeted exome sequencing to diagnose FHS

Patient: The boy was born to nonconsanguineous parents of Chinese Han ethnicity at 38 weeks of gestation with birth weight of 2.4kg, 46cm in length. His parents and sister were clinically normal. He presented with failure to thrive, delayed motor

P3-152

Linear Growth of infants with neonatal and early infantile meningitis

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We analyzed the clinical data and the growth parameters of 50 newborns and young infants (age: 1.6 ± 0.9 months) admitted to our hospital (Al Wakhra Hospital, Department of Pediatrics, Doha, Qatar), between 1-1-2016 to 1-1-2017, with acute meningitis. Anthropometric measurements included weight, length, and head circumference. Length SDS (L-SDS) and body-mass-index (BMI) were calculated and recorded at every clinic visit, every 3 months for 8 ± 2 months.

Results: In this age group of neonates and young infants with acute meningitis fever (84%) and hypoactivity (64%) were the major presenting manifestations. Acute bacterial meningitis (n: 10) was associated with higher morbidity [shock (n: 1), subdural empyema (n: 1) and hydrocephalus (n: 1)]. Cerebrospinal fluid (CSF) examinations showed that infants with bacterial meningitis had significantly higher pleocytosis of mainly polymorphic leukocytes and protein levels, compared to those with aseptic meningitis.

All infants showed normal linear growth and weight gain during the follow-up period (10 ± 2 months). The annualized growth rate of infants = 25.3 ± 3.5 cm per year. All had normal length standard

deviation scores (LSDS) (-0.2 ± 0.9) and none of them had LSDS < -2 . All infants had a normal BMI (16.7 ± 1.8 kg/m²). Head circumference growth was normal in 49/50 infants (43.8 ± 1.8 cm) at 8 ± 2 months. One infant developed hydrocephalus after GBS meningitis. There was no statistical difference in linear growth between infants with aseptic and bacterial meningitis.

Conclusion: Infantile linear growth appears to be normal in all newborns and young infants with both bacterial and aseptic meningitis. However, acute bacterial meningitis in newborns and young infants is still associated with considerably high morbidity and complications.

P3-153

Prevalence of Thyroid Dysfunction and Associated Autoimmune Disorders in Young Children with Down Syndrome (DS); A Cohort Study

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There is an intriguing association between DS and thyroid abnormalities, which include sub-clinical, overt hypothyroidism, hyperthyroidism, and positive thyroid Antibodies. The prevalence of these abnormalities varies considerably depending on the diagnostic criteria and the selected population which includes sample size and age group.

Aim: To measure the prevalence of thyroid dysfunction and associated autoimmunity in children with Down Syndrome (DS)

Patients and Methods: All children (aged 2.3 ± 3 years) with the diagnosis of DS who were seen in the General Pediatric Clinic of HGH during the year 2018 (n =102) were the subjects of this study. Their clinical and laboratory investigations were reviewed

retrospectively including TSH, free T4 (FT4), Thyroid antibodies and associated other autoimmune dysfunction.

Results: Out of the 102 children with DS

(Cutoffs : Normal TSH: 0.13 to 5 mIU/L; Normal fT4: >10 pmol/L; Subclinical hypothyroidism TSH > 5 < 10 mIU/L. Central hypothyroid = low or normal TSH with low fT4. (Thyroid. 2017;27(11):1360)

Conclusion: We documented a higher prevalence of primary (4%) and secondary (2%) hypothyroidism in our young children with DS. Subclinical hypothyroidism and positive thyroid antibodies were found in (30.4%, 28.4% respectively). The difference between our data and other research results in literature can be explained by the younger age of our patients and early screening for thyroid function.

P3-154

NSD2 Mutation in a Family with a New Intellectual Disability and Short Stature Syndrome: a 7.5 Years Follow-up

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Wolf-Hirschhorn syndrome is a genomic disorder caused by 4p16.3 deletion with facial dysmorphology, growth retardation, developmental/intellectual delay and seizures. After 165 kb critical region encompassing NSD2 was identified, most recently,

	Prevalence in DS	Prevalence in Down syndrome children Horm Res Paediatr. 2017; 87(3): 170–178
Number	102	508
Age, Mean (years)	2.3	6.5
Central hypothyroidism	2%	
TSH >10 mIU/L (Isolated Hyperthyrotropinemia)	25.5%	4.5%
TSH > 10 + FT4 <10 (Overt hypothyroidism)	4%	1%
TSH > 5 and < 10 mIU/L (Subclinical Hypothyroidism)	30.4%	10%
FT4 > 19 pmol/L (Hyperthyroidism)	1%	1.6%
Positive Anti Thyroid antibodies	28.4 %	46%
Other autoimmune disorders/antibodies	5.9%	--
Type 1 DM	2%	0.8%
Alopecia areata	2%	
Antiphospholipid antibody +ve	2%	
Congenital Heart Disease	66.6%	68%

three *NSD2* loss of function variants was uncovered in patients with overlapping phenotype with Wolf-Hirschhorn syndrome. In our study, a *NSD2* variant, c.1577dupG (p.Asn527fs*14) was identified in two patients in one family with short stature[W1], intellectual delay and distinct facial features. We followed up this family for 7.5 years and growth hormone therapy was initiated. Our results extended the genetic spectrum of *NSD2* mutation and provide evidence of GH therapy on long-term growth of *NSD2* mutation patients.

P3-155

Turners Syndrome - clinical presentation, genetics, investigation and management: a 10-year review

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Background: Turner syndrome (TS) is characterised by a wide phenotype and age at presentation. We reviewed our over-12s Turner clinic over a period of 10 years to evaluate pattern of diagnosis, co-morbidities and management.

Subjects & Method: Retrospective data analysis of patients with TS who attended the over-12s clinic (2008-2017, n=28). Data is median (IQR) or mean±SD as appropriate.

Result: The age at diagnosis was 10.4(1.9-15.0) years. Presenting complaints were identified in 18 (64.3%) patients: congenital heart disease (CHD) in 2 of 3 diagnosed at birth; short stature in all 9 diagnosed at 1-13.9years; delayed/arrested puberty in 7 diagnosed ≥14years).

Karyotype results were available for 27(96.4%) patients (11 45, XO; 16 mosaic). Those diagnosed at birth had Classic TS (100%) compared to 23% of those diagnosed after infancy.

Twenty-five (89.2%) patients had documented comorbidities; ENT disorders (n=12), CHD (n=5), lymphedema (n=5), renal/urological disorders (n=7), visual impairment (n=5), psychological problems (n=3); thyroid dysfunction (n=3) and coeliac disease (n=1).

The serum oestrogen levels were below detection level in 17(63%) out of 27(96.4%) girls with identifiable results at commencement of oestrogen therapy. The value was 63pmol/l (51.75-95.50) in the remaining 10 (37%) girls. All the 28 girls had elevated gonadotrophins at the commencement of oestrogen therapy.

Raised ALT ($\geq 35\text{iu/l}$) in the absence of clinical symptoms of liver disease was seen both pre- and post-puberty (2/26 and 5/25 respectively) and was unlikely to be related to oestrogen therapy. The 2 girls with pre-pubertal raised ALT remained so after puberty. Raised triglycerides (TGL) noted pre-puberty (2/12) persisted (3/22 post puberty). There was no significant difference in the BMI SDS change of either those with normal and raised ALT or TGL.

Routine referrals as recommended by the TS Consensus Study Group were made for echocardiogram (21, 75.0%), renal ultrasound (17, 60.7%), dental review (5, 17.9%) and to ENT (21, 75.0%).

Twenty-six (92.9%) had growth hormone therapy (GHT), duration 3.7(2.6-5.6) years with an improvement in height-SDS at the end of GHT of 0.3 ± 1.0 . Patients with late diagnosis were relatively

shorter at the start of GHT ($\geq 14\text{years}: -2.9 \pm 0.6$; $\leq 13\text{years}: -2.1 \pm 0.7$; p=0.05) and the final height-SDS difference was significantly different (p<0.01).

Conclusion: TS is diagnosed all through childhood with some age specific presentations. Comorbidities result in a significant disease burden and ENT disorders particularly are common. GHT is associated with an overall positive gain in height-SDS.

P3-156

Growth Status of children and adolescent born Full Term Small-for-Gestational-Age in Korea: Data from the KNHANES-V (2010-2011)

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Background: Currently, little information is available on current growth status according to birth weight at gestational age (BWGA) on Korean adolescents. Herein, the current height and weight of Korean adolescents who were born as small for gestational age (SGA) were compared to those of the non-SGA groups.

Methods: Data from the population-based nationwide Korean survey 5th Korea National Health and Nutrition Examination Survey (KNHANES, 2007-2009), 843 children and adolescents (aged 1-18 years) who had birth data and current anthropometric data were used. Logistic regression analyses were used to estimate ORs (95% CIs) for the associations of SGA and catch-up growth status adjusting for potential infant- and parent-related confounding factors.

Results: From the birth history of adolescents, the prevalence of SGA was 13.9% (n = 193) in male and 12.8% (n = 191) in female,[d2] respectively. SGA children had a chance to have Father's short stature or mother's short stature (OR, 10.42 ; 95% CI, 5.55-19.56). Fifteen percent of term SGA infants failed to catch up in height. Furthermore, SGA children without catch-up growth were at increased risk for short height (OR, 3.85; 95% CI, 1.19-12.47) at 16-18 years of age.

Conclusion: The infants born SGA may be at increased risk for short stature in Korean adolescence.

P3-157

Bardet-Biedl syndrome: a case series

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Introduction: Bardet-Biedl syndrome is a rare autosomal recessive disease, characterized by rod-cone dystrophy, truncal obesity, left foot polydactyly, cognitive impairment, male

hypogonadotropic hypogonadism, female genitourinary malformations, and renal abnormalities. The authors present 3 cases of Bardet-Biedl syndrome diagnosed during pediatric age.

Case Description: Case 1: A 3-year-old girl with a family history of consanguinity was diagnosed with Bardet-Biedl syndrome at the age of 22 months due to the presence of left foot polydactyly, bilateral foot brachydactyly, truncal obesity, developmental delay and left hydronephrosis. Genetic testing was positive for a homozygous mutation in the BBS7 gene. Her annual ophthalmologic evaluation has been showing the presence of astigmatism with no signs of rod-cone dystrophy so far. Post-axial polydactyly was corrected at the age of 8 months. She currently maintains a regular follow-up in the hospital, with nutritional support and speech and occupational therapy.

Case 2: A 12-year old female adolescent with obesity, polydactyly of both feet, clinodactyly of the fifth finger, bilateral foot syndactyly and developmental delay with positive genetic testing was diagnosed at the age of 2 years with Bardet-Biedl syndrome. A family history of consanguinity was present. Apart from an episode of neuroblastoma at the age of 6 months, that was resected at the age of 11 months, she was diagnosed with severe rod-cone dystrophy with macular involvement when she was 7 years old. Due to the progressive and rapid deterioration of her visual acuity, she is currently in need of a system of visual amplification in her daily activities.

Case 3: A 13-year-old male adolescent was referred to the pediatric external consultation due to truncal obesity, severe rod-cone dystrophy with tunnel vision, polydactyly and syndactyly of both hands and feet, hypogonadism and developmental delay. Genetic testing revealed a mutation in the BBS1 gene. Over the course of his follow-up, he developed hepatic steatosis and dyslipidemia requiring oral medication. He maintains a regular follow-up in the nephrology external consultation due to the presence of nephrocalcinosis and the suspicion of the presence of a medullary sponge kidney.

Conclusion: As shown by our case series, Bardet-Biedl syndrome has a significant interfamilial variation. There is currently no cure for Bardet-Biedl syndrome; patients require a symptomatic and preventive approach and a close multidisciplinary follow-up.

great toes, congenital cardiac defects, congenital hypothyroidism, and significantly impaired speech. The c.5124delC (p.L1709Sfs*5) variant affects exon 18, where is the Ser rich region. The clinical and genetic characterization could contribute to the understanding of SBBYSS.

P3-159

Three Cases with Familial Short Stature: Leri-Weill Syndrome

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Introduction Objective: The SHOX gene is located in pseudautosomal region of chromosomes of Xp22.33 and Yp11.32. It plays role in proliferation and differentiation of epiphyseal chondrocyte. Leri-Weill syndrome is observed with loss of an allele, while missense mutations lead to idiopathic short stature without any dysmorphic findings. This report presents clinical features of three cases diagnosed with Leri-Weill syndrome, and their responses to rhGH treatment.

Cases: Clinical and laboratory features of three cases diagnosed with Leri-Weill syndrome are summarized in **Table 1**. Routine examinations regarding short stature of patients were evaluated as normal.

Result: Most cases of SHOX haploinsufficiency are considered to be idiopathic or familial short stature due to the poor clinical findings. SHOX deficiency should be investigated especially in the presence of findings such as shortness of limb and madelung deformity. rHGH treatment is a safe and effective option for improving final height in children with SHOX deficiency.

P3-158

A novel variant of KAT6B caused Say-Barber-Biesecker-Young-Simpson syndrome

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Say-Barber-Biesecker-Young-Simpson syndrome (SBBYSS) is a rare and clinically well-described disease caused by de novo heterozygous mutations in KAT6B gene. Genitopatellar syndrome (GS) is also caused by the mutations of gene KAT6B and shares some common clinical symptoms with SBBYSS. The phenotypic spectrum caused by KAT6B is very broad that some patients cannot be classified as SBBYSS or GS. Herein, we report one de novo heterozygous KAT6B truncating variants c.5124delC (p.L1709Sfs*5) in a 5-year-old girl presenting with severe blepharophimosis, a bulbous nasal tip, dental anomalies, abnormally long thumbs and

Table 1.

	CASE-1	CASE-2	CASE-3
Age	6,2	3,6	1,6
Sex	Male	Male	Female
Complaints	Short stature	Short stature	Short stature
Background	No Characteristics	Asthma	No Characteristics
Similar cases in the family	Mother's height: 143 cm Father's height: 165 cm Target height: 160,5 cm (-2,2 SDS)	Mother's height: 150,8 cm Father's height: 151,6 cm Target height: 157,7 cm (-2,5 SDS) SHOX deletion in father	Mother's height: 150,8 cm Father's height: 151,6 cm Target height: 144,7 cm (-2,8 SDS) SHOX deletion in father and brother
Height (SDS)	101 cm (-3,4)	89,3 cm (-2,85)	75 cm (-2,4)
Weight (SDS)	16.4 kg (-2,02)	16 kg (-0,03)	9,3 kg (-1,33)
BMI SDS	0.4	2.7	0.01
Average Height/Height (Percentile)	0.59 (>95 p)	0.61 (>95 p)	0.58 (>95 p)
Mesomelia	None	None	None
Madelung deformity	Yes	Yes	None
Laboratory-observation			
Bone Age (SDS)	4 years 6 months (-2,08)	2 years (-2,3)	14 months (-1,2)
IGF-1 (ug/L)	198 (22-208)	79.4 (<15-129)	83.9 (18.2-172)
Pre-treatment Annual Growth Velocity (GV)	4.4 cm/year	4.68 cm/year	4,96 cm/year
Peak GH response (ng/ml)	6.33	8.7	5.69
rhGH dose rhBH period	50 mcg/kg/day 2 years 10 months	25 mcg/kg/g 3 years 5 months	35 mcg/kg/day 11 months
Post-treatment Annual Growth Velocity (GV)	9,19 cm/year	10.9 cm/year	9.9 cm/year
Genetic Conclusion	Deletion of 266 Kb with 2 OMIMs in Xp22.33 region.	SHOX deletion at locus Yp11.3	CNV gain with 15 OMIM genes of 1.4MB on the X chromosome.

P3-160**Thyroid Dysfunction in the First Year of Life in Infants with Down syndrome: Linear Growth Over 4 Years**

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Background: Down syndrome (DS) is associated with thyroid dysfunction including both congenital and acquired hypothyroidism (HT). However, data about thyroid function in infants < 1 year with DS is scarce.

The aim of this study was to investigate the prevalence of different thyroid dysfunctions in a cohort of infants with DS (n = 47) (22 M, 25 F) and follow up their linear growth and weight gain for an average of 4 years.

Patients and Methods: Retrospectively we studied thyroid function in a cohort of infants with DS (n = 47) (below 1 year) and followed up their linear growth and weight gain (height SDS (HtSDS), delta HtSDS, BMISDS, and delta BMISDS) for an average of 4 years.

Results: presented in 2 tables

Table 1. Prevalence of thyroid dysfunction in infants with DS < 1 year of age

	Prevalence in DS
Number	47
Age, Mean (years)	0.5 +/- 0.3
Primary Hypothyroidism (low FT4 + high TSH)	1/47 (2%)
TSH > 15 mIU/L	5/47 (11%)
Central hypothyroidism	2/47 (4%)
TSH > 5 and < 15 mIU/L (subclinical hypothyroidism)	23/47 (49%)
TSH < 5 mIU/L	19/47 (40%)
Positive Anti Thyroid antibodies	9/47 (19%)
Other autoimmune disorders/ antibodies	1/47 (2%)
Type 1 DM	1/47 (2%)
Congenital heart Disease (CHD)	36/47

Table 2. Growth of Children with DS categorized according to their primary thyroid function

Groups	age 1	LSD1	BMISDS1	age 2	LSD2	BMISDS2	Delta HTS DS	Delta BMISDS
TSH > 5 -< 15 Mean	0.48	-1.46	-1.04	4.41	-1.99	0.43	-0.53	1.43
	SDS	0.38	1.28	1.38	4.25	0.81	1.14	1.16
TSH < 5	Mean	0.54	-1.75	-0.99	2.54	-1.82	0.33	-0.07
	SDS	0.39	2.51	1.33	1.00	1.53	1.62	1.43
TSH > 15	Mean	0.29	-2.43	-2.77*	4.46	-2.24	0.69	0.20
	SDS	0.31	1.70	1.76	4.69	0.74	0.75	1.72

*p<0.05

Conclusion: Infants with DS < 1 year of age had a high prevalence of thyroid dysfunction. Subclinical HT (TSH > 5 and normal FT4) is the most frequent abnormality in these infants. Both primary and secondary HT are found in these infants. Autoimmunity against thyroid was detected in 19 % of these young infants (early autoimmunity). Infants with TSH > 15 had significantly lower BMISDS and were non-significantly shorter than the other groups ($p= 0.03$ and $p = 0.14$ respectively). Infants with TSH > 15 mIU/L were treated with L thyroxine. After an average of 4 years of treatment, the BMISDS and HtSDS did not differ among the 3 groups.

P3-161**The Effect of Thyroxine Treatment on Linear Growth and Weight Gain in Infants and Children with Down Syndrome (DS) and High TSH versus Children with DS and normal thyroid function: A controlled study**

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Background: Subclinical hypothyroidism is the most common in DS. Thyroxin administration to improve growth early in life is still controversial.

We measured linear growth (BMI, height SDS (HtSDS) and weight gain/day) in 3 groups of infants and young children with Down syndrome (trisomy 21) and divided them retrospectively into 3 groups according to their thyroid function. Group 1 (n = 25) with normal FT4 and TSH, group 2 (n = 20) with high TSH > 5 < 15 mIU/L with normal FT4, and group 3 (n = 12) with TSH > 15 mIU/L and/or FT4 < 9 pmol/L. ANOVA test was used.

Results:

Table 1: Thyroid function in 2 groups of trisomy 21 with high TSH before and after treatment compared to controls.

Groups		Age-1	TSH	FT4	L thyroxine	Age-2	FT4 -2	TSH- 2
Groups		yr	mIU/L	pmol/L	ug/day	yr	pmol/L	mIU/L
TSH > 15 or FT4<9	Mean	3.86	50.75	10.93	34.38	7.73	13.85	8.05
Treated	SD	5.63	38.80	3.47	16.93	5.52	2.14	4.00
TSH >5 <15	Mean	2.88	9.50	13.88	29.32	8.88	14.29	8.14
Treated	SD	2.70	4.83	4.13	9.34	5.04	4.00	3.80
Normal	Mean	1.64	9.80	15.16	NT	4.15	14.16	5.77
NT	SD	2.03	4.06	3.33	NT	2.81	2.45	2.73
P=		0.077	0.000035	0.0032	0.65	0.0008	0.973	0.45

Age 1, 2: before and after treatment, NT = not treated with thyroxine.

Table 2. Anthropometric data in 2 groups of trisomy 21 with high TSH before and after treatment compared to controls.

Groups		Age 1 (yr)	L/HtSDS1	BMISDS-1	Age 2 (yr)	HtSDS2	BMISDS-2	Wt gain/d	Delta HTSDS	Delta BMISDS
TSH > 15 or FT4<9	Mean	3.86	-2.15	-0.77	7.73	-2.39	0.66	9.95	-0.24	1.43
Treated	SD	5.63	1.46	2.63	5.52	1.01	1.69	5.80	1.32	2.49
TSH >5 <15mIU/L	Mean	2.88	-1.57	0.38	8.88	-2.18	1.37	7.67	-0.62	1.23
Treated	SD	2.70	1.04	1.82	5.04	1.27	1.98	5.95	1.09	3.25
Normal TFT	Mean	1.64	-1.90	-0.13	4.65	-2.08	0.59	8.35	-0.17	0.69
No treatment	SD	2.03	1.36	1.68	2.81	0.93	1.48	4.18	0.97	1.41
P=		0.08	0.11	0.0	0.0008	0.47	0.29	0.84	0.211	0.28

Age 1 and 2: before and after treatment.

Discussion: At presentation and after 3 years of treatment with L thyroxine, we did not find a significant difference in linear growth or weight gain in infants and children with DS with high TSH compared to those with normal thyroid function.

Case Report: The proband was 4y6mo old, second born to 3rd degree consanguineous parents and presented with concerns of short stature. His height was 81 cm(z-score -5.1) and weight was 13kg(z-score -1.6). His intelligence was noted to be normal. Phenotypically, he had frontal bossing, arched eyebrows, long eyelashes, fanning ears, short nose and small teeth. Characteristically, he had mesomelic and acromelic shortening with brachydactyly in both upper and lower limbs. There was laxity of joints. The spine seemed grossly normal.

Skeletal survey also revealed acromesomelic shortening and delayed bone age. Investigations revealed a low IGF-1- 18.9 ng/ml (Normal-50-286ng/ml) and had failed two separate growth hormone stimulation tests. The rest of the hormonal profile was normal.

Focused exome sequence analysis revealed an apparently homozygous indel variation in exon -1 of the Natriuretic peptide receptor 2 (NRP2) gene on Chromosome 9 (c.663-664delGCinsAA p.Arg222Ser). This variant has not been previously reported in individuals with this disease and has also not been observed in the general population. It was found to be potentially deleterious by PolyPhen-2 and SIFT bioinformatics tools.

Clinically the proband was suspected to have an Acromesomelic dysplasia-Maroteaux type and it was substantiated genetically by the above finding.

P3-162

Acromesomelic Dysplasia of Maroteaux- an extremely rare cause of short stature

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Introduction: Acromesomelic Dysplasia of Maroteaux (AMDMD) is a cause of severe short stature (final height below-120cm) with shortening of the middle and distal segments of the limbs, caused by homozygous or heterozygous mutations in the NRP2 gene which encodes natriuretic peptide receptor B on chromosome 9p13

Due to concomitant Growth hormone deficiency, he was started on recombinant Growth hormone @0.025mg/kg/day.

On 6 month follow up, he had shown a favourable height gain of +4cm on Growth hormone.

Conclusion: The C-type natriuretic peptide and its receptor NPR-B are recognized as important regulators of longitudinal growth. Variations in the encoding genes (NPR2 gene) must be considered in short stature presenting with acromesomelic skeletal dysplasia. Genetic counselling plays an important part of management in the above disorder.

P3-163

Endocrinological evaluation of male patient with Floating-Harbor syndrome –case report

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Patients with Floating-Harbor syndrome have broad spectrum of clinical presentation, but most of them have short stature, low birth weight, delayed bone age, delayed speech development, typical craniofacial features, anomaly of fingers and toes, cryptorchidism in males, renal anomalies, strabismus.

Case Report: 4 year old male patient with mutation in SRCAP gene Gln2622Ter/- is followed up in our Pediatric Endocrinology Outpatient Clinic since he was one year of age. He was born small for gestation age, with birth weight 2700g in 40Hbd. Phenotype manifestation is: short stature(Z-score is -4,18); weight is in lower limit for age and height. Patient's bone age is significantly delayed (BA: 6 months). He shows some of typical craniofacial features, like triangular face, short philtrum, wide mouth with a thin vermillion border of the upper lip, low-set ears, long nose, furthermore strabismus, brachydactyly, clinodactyly, broad finger tips. He revealed speech development delay especially in verbal communication, but his speech understanding and general development was in quite good level. Assessment of thyroid showed euthyroidism with negative thyroid antibodies, in ultrasound scan thyroid volume was 1,43ml, bilaterally there were two central focal lesions up to 5x5,5mm, noticed and they will be followed up. GH levels were in normal ranges, with peak of 13,3ng/ml during spontaneous nocturnal test. During glucagon stimulation test hypoglycaemia was achieved -46mg/dl w 120 minute; GH peak was 11,9ng/ml. In the same test we estimated adrenal function – cortisol peak was 601 nmol/l. In OGTT glucose levels were low at the beginning 55 mg/dl and elevated to 87mg/dl in 120' minute, insulin peak was 6,5uU/ml in 120' minute. During the OGTT massive glucosuria was revealed. We didn't find renal anomalies nor renal dysfunction. Total cholesterol and LDL were elevated. Sexual development was adequate to age, Tanner stage I, testis 2ml, in scrum. Pituitary MRI scans will be performed and rGH treatment in nearest future will be started for SGA patient.

Conclusions: The patient with Floating-Harbor syndrome didn't reveal endocrinopathies, but SGA, short stature, bone age delay and glucosuria.

P3-164

Longitudinal evaluation of audiological pattern in Turner syndrome

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Objectives: To investigate prognostic markers (age, initial hearing level, karyotype, chronic hormonal therapies, and presence/absence of a mid-frequency dip influence) for hearing loss (HL) in Turner syndrome (TS).

Design: Longitudinal cross-sectional and retrospective study.

Study Population: 61 TS females (age range 4 - 45 yrs), diagnosed by cytogenetic analysis (49,2% monosomy X, 41% mosaicism and 9.8% structural aberration of X chromosome), 90,2% of them treated with growth hormone (GH), 88.5% underwent pubertal induction, 78.7% presented positive otolaryngological (ENT) remote anamnesis.

Methods: ENT anamnesis and physical examination, pure tone audiometry (PTA) (frequencies ranging from 0.25 to 12 Hz) were performed. In each patient, at least 2 PTAs were evaluated through 10 years; 1st and 2nd PTAs were performed at median age of 11 yrs (range 4 – 29) and 26 yrs (range 15-45), respectively. The median follow-up period was 13 yrs (range 10-30).

Results: HL frequency increased from 41 to 59%, sensorineural HL (SNHL) from 18 to 56%, and conductive HL (CHL) from 23 to 36%, from 1st and 2nd PTAs. In young adult patients SNHL, mainly involved the high frequencies, from 8 to 12 kHz. The mid-frequency dip (2-4 kHz), considered as early and predictive sign of future SNHL, had been pointed out only in patients over 12 years (prevalence 16% for worse ear).

Eight TS with CHL at 1st PTA, were normoacusis in the 2nd one.

HL was significantly more common in patients with karyotype 45, X0 (52%) than those with mosaicism (28%) or chromosome X aberrations (20%) ($p = 0.044$).

The logistic regression detected 2 variables that significantly worsen auditory outcomes in TS: GH therapy (Odds 2.5) and a positive ENT remote pathology (Odds 3.0).

The Kaplan-Meier curve confirmed that the risk of HL progressively increased with age; furthermore, a clear increased probability of HL was observed after 15 years of follow-up.

Conclusions: 1) SNHL increased with age; 2) SNHL not always was preceded by a framework of CHL or mid-frequency dip, but it might be preceded by early high frequencies (8-12 kHz) HL; 3) GH therapy and ENT remote pathology resulted significant predictors of HL in TS.

P3-165**Final adult height in a patient with Turner syndrome {46, X, i(Xq)} treated with growth hormone for 10 years compared to her normal dizygotic twin sister and mid-parental height**

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Anthropometric somatotype components show significant resemblance in monozygotic (MZ) and dizygotic twins (DZ) twins within each sex with a greater resemblance within MZ twin pairs than within DZ twin pairs. In many studies a significant positive correlation was found between the parental height and the height of girls with TS.

This girl with Turner syndrome {46, X, i(Xq)} presented at the age of 7.5 years for evaluation of her short stature. Her clinical evaluation revealed normal phenotype with normal cardiac examination. Echocardiography was normal. Karyotyping proved Turner syndrome (46,X,xi(x)(q10). Her bone age was 7 years. Labs revealed normal thyroid profile, renal and hepatic functions. U/S pelvis revealed anteverted uterus (3.9 x 1.5 cm). The right and left ovaries were 0.26 ml and 0.4 ml respectively. Her mid-parental HtSDS = 0.05. Her IGF-ISDS = -2, and her peak GH response to provocation with clonidine was normal (21 ng/dl). She was started on HGH therapy 0.05 mg/kg/day and followed up 6 monthly. Her IGF-ISDS increased to 1.5 and her growth is presented in table. At 12 years of age she was started on low dose ethynodiol diacetate and at 15 years she was started on oral EE 30mcg/levonorgestrel 150mcg therapy. At the age of 17 years her HtSDS = -2.6 on the normal female growth curve and her Ht SDS = 1.3 on the Turner growth curve. Her normal twin sister started menstruation at the age of 13 years and her final adult height attained at 17 years = 161 (HtSDS = -0.14) (fitting with the mid-parental HtSDS).

Discussion: It appears that 10 years of GH therapy and estrogen replacement therapy improved the final height (HtSDS) of this girl to 1.3 above her mid-parental HtSDS and 1.1 SDS above her twin sister HtSDS which corresponds to about 6-7 cm on Turner growth curve.

Age (yr)	Length/Height (cm)	L/HtSDS	Wt (kg)
Birth	49		2.43
7.5	106	-2.8	19.8
GH started			
9	118	-2.56	25
10	123.5	-1.87	28
11	128	-2.2	30
12	133	-2.4	34
GH + E Estradiol			
14	142.5	-2.7	43
15	144.5	-2.7	44.7
16	146	-2.56	51
17	146	-2.6	50
Her Normal twin			
17	161	-0.14	53

Conclusion: In comparison with her normal twin sister, the use of GH and estrogen therapy in this patient with Turner syndrome improved her final adult height by > 1 SDS.

P3-166**Growth hormone treatment and puberty in patient with Pallister-Hall syndrome***Elena Pisareva, Alisa Vitebskaya*

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Background: Pallister-Hall syndrome (PHS) is a rare autosomal dominant disorder characterized by a complex of different abnormalities (polydactyly, bifid epiglottis, hypothalamic hamartoma, imperforate anus). Syndrome is caused by mutations in the GLI3 gene. PHS is associated with hypopituitarism, early or precocious puberty.

Objective: to demonstrate a patient with PHS treated with growth hormone (GH) and gonadotropin releasing hormone analogue (GnRHA).

Result: Our patient is a 11 years old boy. His parental height is 174 cm mother, 180 cm father. He was born at 39 weeks of gestation, with birth length 53 cm, weight 3900 g, multiple abnormalities (imperforate anus, polydactyly, micropenis, cryptorchidism, bifid epiglottis). MRI of brain performed at the age of 7 years demonstrated hypothalamic mass 5,8*4,1*4,9 cm with signal density suggestive of hamartoma. Considering all components, PHS was suspected.

The first endocrine examination was at 7 years. His height was 111,9 cm (SDS -2,35). The bone age was 2,5 years delayed. IGF-1 was < 25 ng/ml. Thyroid and adrenal function were normal. The GH peak after clonidine stimulation was 3,8 ng/ml. The boy was treated with GH 0,033 mg/kg/day with good effect. At the age of 10 years he had a spontaneous puberty. His height was 143 cm (SDS +0,16). Tanner 2. Bone age was accelerated for 1 year. His hormonal status was LH 3,6 mIU/ml, FSH 2,3 mIU/ml, testosterone 4,4 nmol/l, IGF-1 264 ng/ml. At 11 years his height was 151 cm (SDS +0,58). Tanner 3. For 1 year his bone age was accelerated for 3 years. His hormonal status was LH 4,7 mIU/ml, FSH 1,7 mIU/ml, testosterone 26,7 nmol/l, IGF-1 202 ng/ml. To improve his final height GnRHA therapy was added.

Conclusion: Children with PHS can have GH deficiency and GH therapy can achieve a good result. Precocious or early and rapidly progressing puberty can demand GnRHA therapy.

Bloom Syndrome in 7-year-old girl diagnosed with short stature

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Introduction: Bloom syndrome (BS) is a rare autosomal recessive disorder caused by mutations in the *BLM* gene, located on the long arm of the chromosome 15 (15q26.1). The typical symptoms of the disease are short stature, low birth weight, dysmorphic features including long, narrow face (dolichocephaly), micrognathism and prominent nose and ears. Other characteristic features include a rash following sun exposure, hyper-pigmented areas or cafe-au-lait spots on the skin, high-pitched voice, immune deficiency leading to recurrent pneumonia and ear infections, predisposition to the development of cancer and genomic instability. Patients with BS may also have learning disabilities and a predisposition to diabetes.

Case Presentation: We present a 7-year-old girl with hypothyroidism (treated with L-thyroxine 25 µg) referred to the Department of Paediatrics Endocrinology, Diabetology with Cardiology, Medical University of Białystok due to short stature. The patient was born at term (39/40) with a birth weight of 1580g (SDS -4.66) with a length of 44cm (small for gestational age, SGA). From birth, she had recurrent infections of upper and lower respiratory tract, frequently requiring antibiotic treatment. Physical examination revealed substantial short stature (SDS -5.25) and low BMI, dysmorphic features with long narrow face, micrognathism and cafe-au-lait spots on her abdomen and right popliteal fossa. General laboratory tests were normal. Further analysis revealed growth hormone (GH) deficiency with a delayed bone age of 4.5 years. Suspecting a genetic abnormality, we referred her to the 'Genetic Research Analysing Short Patients' (GRASP) team at the Centre for Endocrinology in London, UK.

After a positive opinion of National Coordination Team for Growth Hormone Application the treatment with GH was initiated as for GH deficiency patients (initial dose of GH 0.54 U/kg/week). The growth rate of the patient over 9 months of treatment was 5.4 cm/year (5.8 cm/year prior to GH treatment).

The GRASP team identified a homozygous mutation in *BLM* gene (91306246C>T, c.1933C>T, p.Q645*) which is recognised to cause Bloom syndrome. After we received genetic confirmation of BS, the treatment with GH was stopped due to the risk of cancer development.

Conclusions: Genetic diagnosis in children with short stature and concomitant dysmorphic features is particularly important and some extremely rare syndromes might be a contraindication to GH therapy.

Efficacy of growth hormone treatment in a patient with chronic granulomatous disease, who developed acute myeloid leukemia after bone marrow transplantation

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Background: Chronic granulomatous disease (CGD) is a rare primary immunodeficiency. Growth retardation is a common finding, due to recurrent severe infections and inflammatory complications. Bone marrow transplantation (BMT) can lead to stable remission, with overall pediatric survival rates > 90% after non-myeloablative conditioning transplants. As reported in previous studies, growth rates in CGD recovered following BMT.

Case Presentation: At the age of 8 years, an Egyptian boy affected by CGD, underwent BMT from his healthy HLA identical sister. Previous medical history included recurrent lymphadenitis, osteomyelitis and pulmonary aspergilloma. At that time, his height was -1.51 SDS (according to WHO growth charts), appropriate for target height (-0.68 SDS). A diagnosis of acute myeloid leukemia (AML) was made two years later. He was treated according to AIEOP (Associazione Italiana di Ematologia e Oncologia Pediatrica) AML 2002 protocol and reached complete remission after a second BMT. After one year, he developed chronic hepatic graft versus host disease (GVHD). At the age of 12, in the absence of minimal residual disease in the last 2 years, a deceleration in growth velocity (height -1.85 SDS) was found and growth hormone deficiency (GHD) was diagnosed (first test peak 7.9 ng/ml, second test peak 1.9 ng/ml). GH replacement therapy was started at a dosage of 31 mcg/kg/day, with initial growth improvement. Eight months later treatment was suspended for AML relapse with central nervous system involvement. The boy underwent a third BMT, this time from a matched unrelated donor, with a subsequent stable disease remission. At 14 years, in the absence of minimal residual disease, considering a persistent growth impairment (height -2.64 SDS, growth velocity -5.67 SDS, Tanner stage 1), IGF-1 low levels and 2-year delayed bone age, he resumed treatment with somatotropin at a dosage of 15 mcg/kg/day. Growth rate improved (8.86 cm/year, +4.48 SDS), according to a good spontaneous pubertal progression. At the age of 18, his final height was 165 cm (-1.47 SDS). During GH treatment, IGF-I levels remained in normal range. Maximum GH dosage was 30 mcg/kg/day. Therapy was well tolerated, except for development of mild IFG and hyperinsulinism.

Conclusions: We present a complex case of CGD who developed AML after transplantation. Main growth impairment became evident after AML onset. Despite two leukemic relapses and chronic GVHD associated with negative influences of multiple chemotherapies and pre-transplantation conditioning (but without body irradiation), standard dosage of GH was effective in improving growth and final height.

P3-169

Schaaf-Yang syndrome: Three cases report of MAGEL2 variation and literature review

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Objective: To highlight the clinical characteristics and early genetic diagnosis of Schaaf-Yang syndrome (SYS).

Methods: Three cases were reported and related literature were reviewed.

Results: All the three patients were diagnosed with Schaaf-Yang syndrome attributing to the variation of *MAGEL2* gene. Two of the patients predominantly presented as “language dysplasia”, who was one 2 years and 6 months old boy (reported recently by us) and one 8 months old girl respectively. Another case was a newborn who was delivered by cesarean section because of fetal intrauterine distress. The Apgar score was 5 at the first minute. Her ears were relatively larger than normal infants without auricular, and her nasal root was higher. The newborn’s fingers were overlapping and presented with clenched fists. Genetically, a *de novo* heterozygous c.1640-1641delTT mutation in *MAGEL2* was detected on the boy, which was origin from his father. Bioinformatics analysis showed that a proline-to-arginine amino acid substitution in position 547 of the protein and early presented the stop codon at amino acid 165 behind the variation (p.Pro547Argfs*165). The 8 months old girl had a *de novo* heterozygous c.3745 C>T mutation in *MAGEL2*. Interestingly, her monther carried the same mutation but her father was not detected the specific genetic variations. Bioinformatics analysis showed that a arginine-to-cysteine amino acid substitution in position 1249 of the protein (p.Arg1249Cys). To our knowledge, both of the above variations have not been reported previously. For the newborn, a heterozygous c.1996dupC mutation in *MAGEL2* was detected, and a frameshift mutation was found in the amino acid (p.Q666Pfs*47). Up to now, a total of 45 individuals suffered from SYS have been reported. Among these patients and our cases, the c.1996dupC mutation was the most common type which accounts for 40.4% (19/47), followed by c.1996delC and c.1912C>T, accounting for 10.6% (5/47) and 8.5% (4/47), respectively. It seems that the c.1996delC mutation has more severe clinical manifestations.

Conclusions: The c.1996dupC mutation was the most common type while the heterozygous c.1640-1641delTT mutation and c.3745 C>T mutation in *MAGEL2* are novel variations which have not been described. For children with developmental delay, intellectual disability, neonatal hypotonia, feeding difficulties, joint contracture, and autism spectrum disorder, SYS should be considered after the exclusion of PWS. Gene analysis in *MAGEL2* should be performed, which is of great significance for early diagnosis of SYS.

P3-170

Reevaluation of congenital growth hormone deficiency in adulthood

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Introduction: Congenital growth hormone deficiency (GHD) is a non-exceptional cause of short stature. The objective of our study is to re-evaluate the clinical, biochemical, and evolutive features of congenital GHD in Tunisian south in adulthood.

SUBJECTS/METHODS: We underwent a retrospective study of 48 patients over 16 years old affected by GHD over 28 years (1990- 2018).

Results: Congenital GHD was revealed in 95,8% of cases by a short stature, noticed at a mean age of $9,4 \pm 3,8$ years (2,25-15,5 years). The sex ratio was 1,8. Growth retardation was severe in 91,7% of cases. A delay in bone development was estimated at $3,7 \pm 2$ years (1-12,25 years). Pharmacological stimuli concluded that GHD was total in 91,7% of cases. Other hormone deficiencies were noted in 39,6% of cases. MRI was abnormal in 60,4% of cases: anterior pituitary hypoplasia, pituitary stalk defects and ectopia of posterior pituitary in 86,2%, 44,8% and 34,5% of cases respectively. The majority of our patients (91,7%) received recombinant human growth hormone (GH). 13,6% of those are still under GH. The mean therapeutic dose for patients whose treatment had been stopped was $0,64 \pm 0,07$ IU/kg/week, the mean height gain at the final consultation was $1,8 \pm 1$ standard deviations (SD) (-1, + 3 DS) and only 13% reached their target height. 72,4% of patients who received GH did hit puberty. The biological revaluation of patients receiving GH detected a new hormonal deficiency in 13,6% of cases (corticotrophic, thyrotrophic and gonadotrophic axis in 9,1%, 6,8% and 4,5% of cases respectively). Only one patient with an isolated GHD and a normal MRI restored his somatotrophic axis.

Conclusion: Although it is a rare condition, missing the diagnosis of DGH will result in poor growth and short stature adults. GHD may or may not persist into adult life and associate or not with other hormonal deficiencies. Patients with childhood onset GHD are usually retested in late adolescence or young adulthood thus the importance of a close collaboration between the paediatric and adult endocrinologists during the transition period.

P3-171

Prevalence and etiology of short stature in children between 2-4 years of age born SGA in a tertiary care hospital in a developing country

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Small for gestational age (SGA) is an important cause of short stature in developing countries like India.

Results: 97 children between 2-4 yrs of age who were born SGA were studied over six months and those whose height was below the third percentile on WHO growth charts were classified as short.

The inter-group statistical comparison of distribution of categorical variables were tested using Chi-Square test and inter-group statistical comparison of continuous variables is done using independent sample t test. Underlying normality assumption was tested before subjecting the study variables to t test. In the entire study, the p-values less than 0.05 were considered to be statistically significant. All the hypotheses were formulated using two tailed alternatives against each null hypothesis (hypothesis of no difference). The entire data was statistically analyzed using SPSS ver 21.0, IBM Corporation, USA.

The prevalence of short stature in SGA children in our study is 20.6%. The mean weight (1.16 SDS, p-0.001) and mean head circumference (2.19 SDS, p-0.005) of the children with short stature was significantly less than that of the children without. The age group of 2.6-3 years showed 33.3 % of short stature children compared to other age groups in our study. Lower socio economic status contributed to 27 % of short stature children as compared to 16.3 % and 18.2 % of middle and upper socio economic status respectively. The various antenatal factors contributing to short stature in our study are maternal age, parity and pregnancy induced hypertension. The gestational age of the mother and the mode of delivery of the child also contributed to short stature with 24.2 % for gestational age > 40 weeks and 21.8 % for normal delivery respectively. Our study shows that longer duration of breast feeding and proper supplementary feeding reduce the number of short stature children. The distribution of mean paternal height, distribution of mean maternal height and distribution of mean mid-parental height did not differ significantly between group of cases with short stature and group cases without short stature (p-value>0.05).

Conclusion: Thus it is imperative to recognise failure of catch up growth in children due to these causative factors and provide timely referral of the child to a paediatric endocrinologist.

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P3-172

Pure gonadal dysgenesis with partial testicular development associated with Turner syndrome with SRY

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Turner syndrome is the most common chromosomal disorder in girls. They present classically short stature and delayed puberty. Turner girls with 45,X karyotype show normal female external genitalia. But Turner patients containing 45,X/46,XY mosaicism, or Sex-determining Region Y (SRY) gene may have mixed gonadal dysgenesis with various external sexual differentiation or pure gonadal dysgenesis. Existence of Y chromosome particles in Turner syndrome implies that they have risk of gonadoblastoma. We experienced a short statured 45,X Turner girl with normal external genitalia. Because SRY gene was positive, laparoscopic gonadectomy was performed. The dysgenetic gonads revealed bilateral gonadectomy tissues. The authors report a pure gonadal dysgenesis with partial testicular development associated with Turner syndrome with SRY gene. Screening for SRY gene should be done even though Turner patient have the 45, X monosomy and no evidence of virilization.

P3-173

A case of Wiedemann–Steiner syndrome with central precocious puberty

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Background: Wiedemann–Steiner syndrome (WSS) is a rare autosomal dominant disorder characterized with hypertrichosis cubiti, dysmorphic facial appearance (hypertelorism, thick eyebrows, and narrow palpebral fissures), psychomotor delay, and short stature. WSS is caused by a mutation in the KMT2A gene. The timing of secondary sexual characteristics in patients with WSS is not well known. To our knowledge, two patients (one boy and one girl) with WSS have been reported to have had central precocious puberty (CPP). It has been reported that 20–47% of patients with WSS showed advanced bone age; however, signs of secondary sexual characteristics in these cases were merely mentioned. Therefore, some of the cases with advanced bone age in these reports might have had CPP, although the first reported patient with WSS who showed advanced bone age did not show signs of secondary sexual characteristics.

Case Presentation: A female patient was born at 39 weeks of gestation with a weight, height, and head circumference at birth of 2712 g (+0.15 SD), 47.5 cm (-0.69 SD), and 29.0 cm (-3.06 SD), respectively. She has had hypertrichosis on her arms and legs since birth. She showed hypertelorism, narrow palpebral fissures, and arched and thick eyebrows. Her psychomotor development was delayed with head support obtained at 7 months, and she was able to sit stably at 10 months, walk independently at 3 years, and speak her first words at 5 years. She was referred to our endocrinology outpatient clinic at 9.3 years of age with a history of pubic and axillary hair development over several months. Her breast pubertal status was Tanner stage 3 or 4, and her bone age was advanced at the first visit. Her levels of luteinizing hormone and follicle-stimulating hormone were elevated at 0.7 and 3.3 mIU/mL, respectively. Menarche occurred at 9.6 years of age, and the diagnosis of CPP was made. Her head MRI showed no brain tumor. She did not receive luteinizing hormone-releasing hormone analogue treatment at the time. Her adult height was 126.0 cm (-6.1 SD) at 17 years of age. We identified a novel, *de novo* splicing mutation (c.4012+1G>C) in the *KMT2A* gene by trio whole-exome sequencing, thus confirming the diagnosis of WSS.

Conclusions: CPP should be considered as a rare complication of WSS.

Conclusions: DS, trisomy 21 is the most common birth defects and are more likely to accompany cardiac complications such as ASD, VSD, and PDA.

P3-175

McCune Albright Syndrome: Two cases with different clinical courses

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McCune-Albright syndrome consists of pigmented skin patches, polyostotic fibrous dysplasia, and a variety of endocrine disorders. Café au lait spots are characteristic skin lesions that reflect the onset of the somatic mutations in melanocytes during embryonic development. Polyostotic fibrous dysplasia is caused by activation of the parathyroid hormone receptor pathway in bone. Hormonal hypersecretion is the result of constitutive cyclic AMP production caused by inactivation of the GTPase activity of G_sa. The G_sa mutations occur postzygotically, leading to a mosaic pattern of mutant expression. McCune-Albright syndrome affects males and females in equal numbers. The disorder is estimated to affect 1 in 100,000 to 1 in 1,000,000 individuals in the general population. Because the disorder is difficult to diagnose, affected individuals may go undiagnosed or misdiagnosed, making it difficult to determine the true frequency of MAS in the general population. Previously MAS was determined as a condition that had three clinical features, such as café au lait spots, fibrous dysplasia, and hyperfunction of an endocrine gland. Recently McCune Albright syndrome consists of at least two of the following above.

We report two cases with MAS to emphasize that all patients with pigmented skin patches should be evaluated to exclude other manifestations of MAS. Our cases supports the statement that only two of clinical characteristics mentioned above, are sufficient to be present to consider MAS.

P3-174

Population prevalence of Down's syndrome and cardiac complications in South Korea: Based on National Health Insurance Service (NHIS)

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Backgrounds: There is a no reliable population-based prevalence data of Down's syndrome (DS) in South Korea. In the present study, we try to estimate the incidence and prevalence of DS and cardiac complications in South Korea using data of National Health Insurance Service (NHIS) data and Rare Diseases Registry.

Methods: We collected the data on DS patients who registered in the Rare Diseases Registry (RDR) between 2006 and December 2015. During this period, the total number of registered DS cases and the number of new registrations each year were identified. To estimate the prevalence of DS, the size of the Korean population in 2015 was ascertained from resident registration data with respect to population data gathered by the Korean Ministry of Security and Public.

Results: The prevalence of Down syndrome (per 100,000) was 2.0322 in 2006, 2.2262 in 2007, 2.6332 in 2008, 3.0711 in 2009, 2.7468 in 2010, 2.8962 in 2011, 3.0376 in 2012, 3.2481 in 2013, 3.8844 in 2014, 4.0272 in 2015. In 2015, the number of DS patients was 2,077 out of the total population of 51,574,044 South Koreans. The death rates (per 1,000) of DS were 5.996 in teenagers, 7.602 in twenties, 7.472 in thirties, 54.7 in forties, 115.18 in more than fifties. The incidence rates (per 1,000) of DS combined congenital heart diseases were higher than control group (ASD, 21.50 vs. 0.27; VSD, 9.65 vs. 0.20; PDA, 8.97 vs. 0.07).

P3-176

Turner syndrome with neonatal revelation: knowing how to think about it

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Introduction: Turner's syndrome (TS) is a rare genetic disorder related to the total or partial absence of an X chromosome, affecting 1/2 500 newborns of female sex. It associates almost steadily a delay in stature and ovarian failure with infertility. The other anomalies are inconstant: morphological features of variable intensity, associated malformations and an increased risk of subsequent acquired diseases. The diagnosis of certainty is established after the completion of a blood karyotype.

Observation: We report the case of a newborn female, the first born of a non-consanguineous couple. Premature 35 SA, born vaginally with intra-uterine growth retardation. The diagnosis was evoked before the IUGR associated with an evocative physical aspect: a lymphoedema of the extremities, a brief and wide short neck, a low implantation of the hair and the ears. Cardiac Doppler ultrasound revealed severe hypoplasia of the aortic isthmus. The rest of the malformation report was without anomalies. The standard karyotype returned to a monosomy of the X chromosome (45 X0).

Comment: The signs of the turnerian phenotype are very variably present. Our patient has neonatal Bonnevie-Ullrich syndrome. The post-natal karyotype was able to confirm the diagnosis, which will allow regular follow-up and adequate multidisciplinary management, especially hormonal treatments for growth optimization and pubertal induction.

Conclusion: TS is a rare genetic disease. The antenatal diagnosis is feasible. Interest of genetic counseling. The care is multidisciplinary.

P3-178

Long-term effect of growth hormone treatment on the onset and progression of scoliosis in children with Prader-Willi Syndrome

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Context: Most children with Prader-Willi syndrome (PWS) develop scoliosis. Scoliosis has a prevalence of 80% in children with PWS older than 10 years, who were not treated with growth hormone (GH). GH is an approved treatment for children with PWS and improves psychomotor development and body composition. The onset and progression of scoliosis are generally associated with an accelerated growth velocity and GH treatment might cause accelerated growth. Since GH treatment has also been shown to increase lean body mass, it might counteract the effect of the accelerated growth on scoliosis development. A previous study supported this hypothesis, as no difference was found in onset of scoliosis and curve progression between GH-treated children with PWS and controls. However, this study had only a follow-up period of two years. There are, to our knowledge, no studies about the long-term effect of growth hormone on the onset and progression of scoliosis in children with PWS.

Objective: To investigate the effects of 8 years GH treatment on the onset and progression of scoliosis and to assess whether there are correlations between serum IGF-1 levels, lean body mass, the onset of puberty and the development of scoliosis.

Design: Prospective cohort study during 8 years of GH.

Setting: Dutch PWS Reference Center.

Intervention: All children were treated with GH 1 mg/m²/day (\approx 0.035 mg/kg/day).

Methods: Every year standardized x-rays of the spine are performed in children with PWS. The Cobb angles were measured by two independent experts.

Main Outcome Measures: Onset of scoliosis, determined as a Cobb angle of 10° or higher, and progression of the scoliotic curve, expressed as the change in the Cobb angle during 8 years of GH.

Results: 90 children with PWS were treated with GH for 8 years. The statistical analysis are in progress. We will have the results of this study early July 2019, so we can present them during the ESPE 2019 meeting in Vienna. We hypothesize that, in children with PWS, 8 years of GH treatment has no negative effects on the onset and progression of scoliosis in children with PWS.

P3-177

Endocrine and Mammary Disorders in Girl with Cornelia De Lange Syndrome (Case History)

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Cornelia de Lange syndrome is a genetic disorder with physical, cognitive, somatic and endocrine disorders.

Objective: To study endocrine and mammary disorders in girl with Cornelia de Lange syndrome.

Objective and Hypotheses: We describe a clinical case of Cornelia de Lange syndrome in girl, 10 y.o.

Method: Total examination (including mammological and gynecological examination), hormonal analysis, thyroid, mammalogical and gynecological ultrasound examination (USE), boneageX-ray.

Results: External examination data: brachycephaly, marble skin, a small nose, long philtrum, thin upper lip, downturned mouth, micrognathia, ptosis, strabismus, unibrow (synophrys), small hands and feet, short and incurved fifth fingers (clinodactyly), partial joining of the second and third toes, hypertrichosis, umbilical hernia. Mental development: disorder of intellectual development (imbecility). Physical development: height 130.5 sm, SDS -0.9; weight 23 kg, BMI 14.2 kg/m². Sex development: Tanner II (thelarche).

Echocardiography: tricuspid valve prolapsed. Thyroid examination: palpable and visible struma, USE (goiter I),isolated hypothyroxinemia. Mammological examination: nipple hypoplasia, USE (bilateral cystsinareolaarea). Gynecological USE: the normal sizes of the uterus and ovaries. BoneageX-ray: the bone age is 8.5 years.

Conclusion: Feature of this case were endocrine (isolated hypothyroxinemia) and mammary disorders (bilateral cystsinareolaarea).

Multisystem Endocrine Disorders

P3-179

Clinical and molecular characteristics of pediatric patients with multiple endocrine neoplasia (MEN)

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Purpose: Multiple endocrine neoplasia (MEN) is a rare, autosomally dominantly inherited cancer syndrome caused by a mutation in *MEN1* or *RET* gene. Identification of the genetic causes of the MEN is critical because genotype provides information on timing of prophylactic surgery in patients with MEN type 2 who have clinically silent tumors. Therefore, this study investigated clinical phenotype and molecular characteristics of children with MEN in a single academic center.

Method: This study included eight children with MEN from seven unrelated families who were diagnosed prior to the age of 18 years between March 2008 and March 2019. Clinical and endocrine characteristics were analyzed by retrospective chart review. Molecular analysis of the *MEN1* or *RET* gene was performed according to the clinical phenotype and family history.

Results: Eight patients from seven families were genetically confirmed with MEN, including MEN type 1 (n = 1), MEN type 2A (n = 6), and MEN type 2B (n = 1). Seven patients had family members with MEN, while only one patient with MEN type 2B occurred sporadically by a *de novo* mutation in *RET*. A 10-year-old girl presented with hypoglycemia due to pancreatic insulinoma, and finally diagnosed with MEN type 1. The patient harbored a known heterozygous mutation of c.852-2A>G in *MEN1*, which was inherited from her father. A 6-year-old boy with MEN type 2B initially manifested tongue neuroma and underwent prophylactic thyroidectomy because of the highest risk mutation at codon 918 in *RET*. Six patients with MEN type 2A had family members of mutation in *RET* and were diagnosed by genetic screening during asymptomatic period. A heterozygous mutation at 634th codon was identified in unrelated 4 families with MEN type 2A: c.1900T>C (p.C634R) in 3 families and c.1901G>A (p.C634Y) in one family. The remaining one patient with MEN type 2A harbored a heterozygous mutation of c.1891G>T (p.D631Y) in *RET*. Three children underwent prophylactic thyroidectomy, and the other patients with *RET* p.C634R mutation were recommended to undergo prophylactic thyroidectomy.

Conclusions: The *RET* gene mutation at codon 634 was the most prevalent in our patients. Genetic screening should be considered in children with family history of MEN for early diagnosis and treatment of hereditary endocrine tumors. Patients with any of the genetic syndromes require lifelong tumor surveillance to facilitate early tumor detection and treatment of associated neoplasms.

P3-180

APECED Syndrome in Childhood: Rare Clinical Presentations to Keep in Mind

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Introduction: APECED Syndrome; is a rare, autosomal recessive disease caused by mutations in the autoimmun regulatuar AIRE gene on the chromosome 21. Although classical triad is mucocutaneous candidiasis, hypoparathyroidism and adrenal insufficiency; endocrine / non-endocrine involvement may also be seen. Possible involvement should be evaluated without any clinical signs. We report a case of APECED syndrome with autoimmune hypophysitis secondary to growth hormone deficiency and autoimmune asplenia.

Case: A 12.5-year-old male patient diagnosed with hypoparathyroidism in another center and whose previously unidentified IVS3-3C> G (c.464-3C> G) homozygote mutation in the AIRE gene was referred to our clinic. When he presented with a history of mouth thrush and fatigue when he was eight years old; it was learned that calcitriol treatment was started with the diagnosis of hypoparathyroidism In physical examination; his body weight was 35.9 kg (-1.86 SDS), height 140 cm (-2.65 SDS), diffuse vitiligo, hypopigmentation in the hair, photophobia, and 8 ml testes. The patient was admitted for further screening. Hashimoto thyroiditis-euthyroid phase (no goiter / nodule), primary adrenal insufficiency (Cortisol: 8.1 µg/dL, ACTH: 568 pg / ml), autoimmune hemolytic anemia (Coombs positive anemia), autoimmune asplenia (USG spleen was not observed, scintigraphy, non-function spleen), autoimmune hypophysitis (infundibulum thick / pituitary heterogeneous) and growth hormone deficiency were detected. Hydrocortisone, growth hormone treatment, penicillin prophylaxis, protective vaccination program was started.

Conclusion: APECED syndrome has a wide clinical spectrum. Keeping rare clinical presentations in mind will reduce the morbidity and mortality of the disease.

P3-181

Phenotype and clinical course in three individuals with Multiple Endocrine Neoplasia Type 2A due to a *RET* gene mutation

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Background: Mutations in the *RET* gene have been described in subjects with multiple endocrine neoplasia Type 2 (MEN 2A). MEN 2A is a rare autosomal dominant disorder characterized by tumors of the C cells of the thyroid, adrenal medulla and

parathyroid glands. Patients develop either C-cell hyperplasia or medullary thyroid cancer, pheochromocytoma, and in some cases hyperparathyroidism.

Objective/Method: To describe the phenotype and clinical course in three family members with MEN 2A syndrome. A *TGC/CGC RET* gene mutation (codon 634, exon 11) was identified in two of these subjects and was associated with their condition.

Result: We report of three individuals diagnosed with MEN 2A syndrome. The proband was a 4-year-old girl, that has been followed-up in our Department in the presence of a significant family history of MEN 2A syndrome.

Her mother, 31 years old, suffered from MEN 2A associated with a *TGC/CGC RET* (codon 634, exon 11) gene mutation. She had metastatic medullary thyroid cancer and had been treated with total thyroidectomy and surgical excision of cervical lymph node metastases as well as bilateral adrenalectomy for pheochromocytomas and radio frequency ablation of hepatic lesions. She now receives replacement treatment with levothyroxine, hydrocortisone and fluorohydrocortisone tablets.

The maternal grandfather was diagnosed with insulin dependent Diabetes mellitus and diabetic ophthalmopathy at 33 years of age. Further laboratory and imaging studies revealed medullary thyroid cancer with multiple hepatic metastases and unilateral pheochromocytoma. He underwent total thyroidectomy and lateral adrenalectomy. Three years later he presented with a contralateral pheochromocytoma, which was inoperable, due to diffuse hepatic metastases and the patient died at 36 years of age.

The molecular genetic testing, that was performed by the 4-year-old female patient identified, that she harbored the same *RET* gene mutation as her mother. At the age of 5 years and 7 months the calcitonin levels after pentagastrin stimulation were found increased and a prophylactic total thyroidectomy was performed due to her genetic risk. The histologic examination showed c-cell hyperplasia. She presents regularly for evaluation, since she is in high risk of developing pheochromocytoma and hyperparathyroidism.

Conclusion: Pheochromocytoma and thyroid carcinoma are indications for detailed clinical and genetic examination of all family members. Subjects with MEN 2A may exhibit a rapid progression and carriers of MEN 2A associated mutations need regular monitoring because of their genetic predisposition to tumor development.

hypoparathyroidism and autoimmune adrenalitis. The mutations in the localized autoimmune regulator gene (*AIRE*) at 21q22.3 present the etiological cause.

Objective: In this case report, two siblings case who were diagnosed with OPS1 with different clinical findings except classic triad were presented.

Case 1: The 16 year old male patient was admitted with short stature. His height was shorter than his peers since his infancy. The target height was calculated 160.3 cm (-2.58 SDS). No constitutional history was found in the family. On physical examination, height 143 cm (-4.46 SDS), weight 32 kg (-3.17 SDS), testicular volume 3/3 ml, pubic hair was Tanner stage 1. In the other system examination, alopecia totalis, vitiligo, dystrophic changes in the nails and oral candidiasis were found. In laboratory examination, glucose: 525mg/dL, TIT: ketone (-), glucose (++) HbA1c: 7.4%, C-peptide: 0.81ng/mL, AntiGAD 37U/mL (N, <10), anti-insulin antibody 2.6U/mL (N, <10) was determined and the patient was diagnosed with type 1 DM. Due to the accompanying clinical findings, OPS was considered and the examinations of which results were shown in Table 1 were performed.

Case 2: The 12-year-old girl who is sibling of the case 1 had been followed-up at our outpatient clinic with a diagnosis of hypoparathyroidism since the age of three years; and had been monitored with oral elemental calcium, calcitriol and sevelamer treatments. On her physical examination, weight: 46.8 kg (-0.02 SDS) height: 152.5 cm (-0.37 SDS), breast development was Tanner stage 1. Dystrophic changes were present in the finger and toenails. No additional pathology was determined in the other system examination. The results of the laboratory examinations are shown in Table 1.

Clinical Course: Type 1 DM, mucocutaneous candidiasis, alopecia, vitiligo, ectodermal dystrophy observed in the first case and hypoparathyroidism, ectodermal dystrophy and autoimmune thyroiditis were observed in the second case. c.769C>T nonsense homozygous mutation was detected in the sixth exon of the *AIRE* gene in both patients. Patients were provided outpatient clinic observation in case of possible emerging endocrinopathy.

Conclusion: It should be kept in mind that (1) main cardinal findings of OPS 1 may develop in different time periods, and (2) adrenal insufficiency and other autoimmune pathologies (hypogonadism, diabetes, vitiligo, thyroiditis, hypophysitis, chronic atrophic gastritis, malabsorption etc.) should be closely monitored in terms of their development.

P3-182

Two Siblings Case with Diagnosis of Autoimmune Polyglandular Syndrome Type 1

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Introduction: Autoimmune polyglandular syndrome type 1 (OPS1) is characterized by chronic mucocutaneous candidiasis,

P3-183**High demand for collaborative work between paediatric endocrinologists in Arab countries**

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Introduction: The Middle East and North Africa (MENA) region has witnessed increasing number of researchers over last decade; for example, in-between 2015 and 2016, the number of researchers (in full time equivalent) per 1 million inhabitants was 2.4K in UAE, 1.1K in Morocco, 680 in Egypt, 604 in Qatar and 242 in Oman. Research and Development investment among Arabic countries was the highest in Tunisia, Egypt, Morocco, Saudi Arabia and the United Arab Emirates, ranged from 0.6% to 1.0% as a proportion of the Gross Domestic Product (GDP)¹. Collaborative strategies that pool resources and knowledge are thought to be vital especially when it comes to rare diseases².

Aim: To identify the demand for collaborative work amongst paediatric endocrinologists who attended the ASPED-ISPAD Lilly Diabetes Academy between 11-13 April 2019.

Methods: An online survey was cascaded to all participants of the above-mentioned educational activity, excluding the faculty member and guests.

Results: 73 participants in the Academy received the survey questionnaire of whom 44 (60%) responded. 48% were consultants, 41% trainees, 9% specialty doctors and 2% psychologists. 75% of respondents were practicing paediatric endocrinology, 23% in general paediatrics and 2% in adult endocrinology. The respondents were from 15 different countries of MENA. All of them (100%) emphasised their interest and eagerness for collaborative work.

Conclusion: As medical research is advancing and researchers are increasing worldwide. This questionnaire study shows the eagerness of our clinicians and researchers to work collaboratively. Therefore, we would encourage the endocrine societies to take a lead in overviewing research projects and opportunities for collaborative work, adopting the hub-and-spoke model to give extra help and guidance to researchers, especially those who are still developing their careers. This approach may improve research engagement resulting in better participation and outcomes.

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P3-184**Eosinophilic Ascites: a rare complication of autoimmune polyendocrinopathy**

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Introduction: Autoimmune polyendocrinopathy syndrome (APS) is an inherited rare autosomal recessive disorder caused by mutations of the *AIRE* (autoimmune regulator) gene with organ-specific autoimmune destruction of several, mostly endocrine. APS patients may develop autoimmune enteropathies and other intestinal dysfunctions.

Aim: We describe a case of eosinophilic ascites in a nine-year-old girl with APS.

Subjects and Methods: The patient presented at the Emergency Unit with a four-day-history of a distended and painful abdomen, constipation and epigastric pain. She had a history of a parasitic infection due to Ascaris and giardia lamblia while living in Albania treated with antiparasitic agents and a three-year history of autoimmune hypoparathyroidism and Addison's disease for which she was on hydrocortisone, fludrocortisone, calcium supplements, and VitD. She was afebrile, had a distended abdomen and epigastric tenderness; no blood in stool, no vomiting. Her growth normal, Tanner stage 1.

Results: Urea & electrolytes, liver function tests, bone profile, immunoglobulins, urine were normal, CRP and ESR mildly increased, D-dimers 342 ng/ml (<500ng/ml). Thyroid function normal, PTH 0.8(1.58-6.03pmol/l), ACTH 75.1(10-60pg/ml). Antibody(ab) screen: abs to parietal cells positive (1/40), antinuclear antibody (ANA) positive (1/80), adrenal abs positive (1/80). Immunophenotype: increased CD3+/CD4+, low CD3-/CD (16 + 56)+ lymphocyte counts compared to the child's age. Antibodies for parasites (Echinococcus, Toxoplasma, Toxocara) and stool cultures negative. Endoscopy and biopsy showed mild gastritis and duodenitis, colonoscopy was normal. Abdominal X-Ray: increased amount of stool in the large bowel. Abdo CT and MRI: inflammation and fluid in the abdomen, around the stomach, liver, caecum and descending colon, mild spleen enlargement. She received a three-week treatment with laxatives, probiotics, omeprazole, metoclopramide, erythromycin, metronidazole, amikacin, and ceftazidime with a positive response and a gradual reduction of CRP and ESR. However, no reduction of fluid was noted on ultrasound. Abdominal biopsy showed eosinophilic ascites (abundant eosinophils and their precursor forms); a 10-day course of albendazole was given with no improvement. Diagnostic laparoscopy and drainage showed a liver cyst and multiple other cysts around the liver and abdomen area, full of fluid. One year later the patient has recovered, atrophic gastritis persists along with the other endocrinopathies and mild hyperthyrotropinaemia.

Conclusions: The eosinophilic ascites was probably caused by the original parasitic infestation. Autoimmune gastrointestinal disorders, which are relatively common among APS patients, are due to the immune reaction to the endocrine cells of the stomach and intestine. We believe that this was the case in our patient.

P3-185

Final height and endocrine complications in patients with β-thalassemia intermedia: (TI) Our experience in non-transfused versus infrequently transfused patients and correlations with liver iron content

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We evaluated the final height and the endocrine complications encountered in young adult patients with Thalassemia Intermedia (TI) followed at Hematology Section, Doha (Qatar) in relation to the liver iron content (LIC) in non-transfused versus infrequently transfused TI patients.

Patients and Methods: This retrospective cohort study was performed on 28 young adults with TI who were randomly selected from the Hematology clinic, National Centre for Cancer Care and Research, Hamad Medical Corporation of Doha (Qatar).

Group 1 included 9 patients who did not receive any blood transfusion and Group 2 included 19 patients who infrequently received a blood transfusion.

Data recorded from charts included demographic characteristics, transfusion frequency, history of chelation therapy, and splenectomy), auxological and pubertal data [growth percentiles and pubertal stages, and body mass index (BMI), laboratory data and target organ complications (including endocrinopathies and liver disease). Iron overload was assessed by direct (liver iron content; (LIC) and indirect methods; serum ferritin (SF), and bone mass index (BMA) by dual-energy X-ray absorptiometry (DXA).

Results: Short stature [Final Height (Ht) SDS < -2] occurred in 25% of patients with no difference between the two groups of patients. (IGF-1) SDS was low in 35.7 % of patients with no statistical difference between the two groups. Impaired fasting blood glucose occurred in 17.8% of patients, diabetes mellitus in 25% and hypogonadotropic hypogonadism in 10.7% of them. Morning

cortisol was low in one patient. No thyroid or hypo-parathyroid abnormalities were detected in any patient. Liver iron content (LIC) > 15 mg/g dry weight and SF > 2,000 ng/mL were detected in 75% of the patients. Both LIC and SF were significantly higher in the transfused group (Group 2). High liver enzyme level (ALT) was detected in 42.8 % of patients. Total and fetal Hb was significantly higher in group 1 versus group 2. Osteopenia was diagnosed in 14.3% of patients. Females had significantly better final height SDS, higher IGF-1 SDS, lower LIC and fasting blood glucose level compared to males. Ht-SDS was correlated significantly with IGF-1 SDS. LIC was correlated significantly with the SF level. ALT concentrations were correlated significantly with LIC and SF levels. Total and fetal Hb did not correlate significantly with Ht-SDS or IGF-1 level.

Conclusions: A significant number of TI patients have high LIC, short stature and endocrine disorders. We also recommend close monitoring of endocrine and other complications, according to the international guidelines.

P3-186

Variable expressivity in three generation from a Colombian family with multiple endocrine neoplasia with mutation c.482G>A (p.Gly161Asp) in the gene MEN1 not described in Colombia

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Introduction: Multiple endocrine neoplasia type 1 is an autosomal dominant illness caused by mutations in the gene menina (MEN1) with high penetrance, characterized by neoplasia

Gender	Age	First Tumor	Hipophysis	Thymoma	Windpipe or Lung	Pancreas	Mutation p.Gly161Asp
M	10	Parathyroid	Prolactinoma				+
F	9	Parathyroid					+
F	40	Parathyroid	Adenoma		+	+	+
M	28	Parathyroid	Growth Hormone Prolactin			+	+
M	46	ND		+			ND
M	44	ND		+			Died
F	75	Parathyroid					+
M	53	Parathyroid					+

M: Male F: Female ND: not determined

parathyroid glands, anterior pituitary, endocrine pancreas and duodenum. Although it has been associated with other types of cancer like breast cancer.

Methods and materials: Clinical analysis, mutational and sequencing report Sanger from gene MEN1 are reported to 6 patients with neoplasia within a large family 15 members (three generations), with 8 members affected.

Outcomes:

Analysis and Conclusions: The 66% of the adults population debited with parathyroid pathology. And the 100% of the children affected. The 33% of the adults showed timoma.

The presence of the c.482G>A (p.Gly161Asp) mutation in MEN1 gene were confirmed by Sanger sequencing in all patients. Therefore, this family with hereditary multiple endocrine neoplasia demonstrate an autosomal dominant inheritance with complete penetrance and high expressivity and is recommend to look always for a parathyroid affection as the first demonstration in the carriers.

All the bioinformatic tools used to predict the mutation effect indicates that the substitution of glycine for aspartic acid at position 161 of MEN1, potentially affect protein structure and function since it is an aminoacid highly conserved between species and is located in a region of interaction with important proteins for the regulation of gene transcription and the progression of the cell cycle, which demonstrates the pathogenic potential of the variant. Although this mutation in MEN1 gene was previously reported by one single Japanese family, it has not been described in Colombia.

180-360mg/dl, insulin was injected many times after meal and infusion sets in insulin pump were not changed regularly, in spite of diabetes training. HbA1c was from 7 to 10%, DDI was in range 0,4-0,8j/kg. In 4th year of life we transferred the patient to insulin multiple injections due to mother's uncooperation. Appointments in outpatient clinic were very irregular.

Conclusions: Difficulties in treatment in the patient could result from clinical presentation of GATA6 mutation and also from problems with cooperation with patient's parents.

P3-188

Endocrinopathies and linear growth in adolescents with β-thalassemia intermedia in Relation to liver iron content

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We evaluated the linear growth and some endocrine function in 10 adolescents with Thalassemia Intermedia (TI) followed at Hematology Section, Doha (Qatar) in relation to the liver iron content (LIC).

Patients and Methods: This retrospective cohort study was performed on 10 adolescents with TI who were randomly selected from the Hematology clinic, National Centre for Cancer Care and Research, Hamad Medical Corporation of Doha (Qatar). 8 infrequently received a blood transfusion. And 2 did not receive blood transfusion.

Data recorded from charts included transfusion frequency, history of chelation therapy, and splenectomy. Auxological data were recorded as well as the pubertal stage. Laboratory data and target organ complications (including endocrinopathies and liver disease were recorded at the last clinic visit. Iron overload was assessed by FerriScan (liver iron content; (LIC) and indirectly by measuring serum ferritin concentration (SF). Bone mineral density (BMD) was assessed by dual-energy X-ray absorptiometry (DXA).

Results: Short stature [(Ht SDS < -2] occurred in 3/10 (30%) with a mean HtSDS = -1.95 +/- 0.7. (IGF-1) SDS was < -2 in 3/10 with a mean = -1.12 +/- 0.9. Impaired fasting blood glucose occurred in 2/10 and diabetes mellitus in 1/10. Delayed puberty occurred in 1/10. Morning 8 AM cortisol was normal (mean = 398 +/- 111). No thyroid or hypo-parathyroid abnormalities were detected in any patient. Free T4 was normal in all patients (mean = 13.2 +/- 1.19 pmol/L). Liver iron content (LIC) > 15 mg/g dry weight and SF > 2,000 ng/mL were detected in 7/10 of patients. High liver enzyme level (ALT) was detected in 3/10 of patients. Osteopenia was diagnosed in one patient. Ht-SDS was correlated significantly with IGF-1 SDS ($r = 0.45, p < 0.05$). LIC was correlated with IGF-I SDS and HtSDS ($r = 0.51$ and 0.5 respectively). ALT concentrations were correlated significantly with IGF-I levels ($r = 0.8, p < 0.01$).

Conclusions: A significant number of TI adolescents on occasional blood transfusion have high LIC, short stature and dysglycemia. Regular monitoring for these abnormalities is highly recommended.

P3-187

Difficulties in hypothyroidism and diabetes treatment in patient with GATA6 gene mutation – case report

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Introduction: Patients with GATA6 gene mutations have broad spectrum of clinical presentation, but most of them have pancreatic agenesis or hypotrophy, exocrine pancreatic insufficiency, insulin-treated neonatal diabetes and cardiac malformations. Some of them have significant neurocognitive deficits, hypopituitarism, hypothyroidism, gut abnormalities, biliary atresia, gallbladder agenesis.

Case Report: The 5.5 year old female patient with mutation R493X in GATA6 gene is followed up in our Pediatric Diabetology Department since she was diagnosed with diabetes in first week of life. Her phenotype manifestation is: pancreatic hypotrophy, insulin dependent diabetes, exocrine pancreatic insufficiency required enzyme supplementation, meconium ileus, tetralogy of Fallot requiring surgery in second year of life, severe hypothyroidism, psychomotor delay. Due to difficulties in cooperation with her mother, very high levels of TSH between 1,2 and 1800uU/ml and abnormal levels of fT4 between <5-23 pmol/l were observed. Mother was educated about L-tyroxin supplementation in doses between 2ug/kg to 5ug/kg, but many times she didn't give the medication to her child. Additionally problems with insulin treatment were observed. Average glucose levels were between

P3-189

Bardet-Biedl syndrome: Not only what but also how matters?

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Bardet-Biedl syndrome (BBS) is a multiorgan genetic disease which is a part of ciliopathies. The HAS (Haute Autorité de santé) published in March 2019 a new National Diagnostic and Care Protocol for Bardet Biedl syndrome. However, in practice, we face the difficulties of screening and multidisciplinary care of different complications.

We report our experience with siblings composed of an eight-year-old boy and an 18-month-old girl suffering from BBS. Our objective is to manage obesity, hypogonadism, vision disorders, with intellectual disability and behavioral disorders.

While the SBB clinic seems well defined, the genetic determinism of BBS remains complex. There is a need for an early diagnosis to guide the patient and overcome medical and social problems.

Because of severe growth impairment by the age of 3.4years (HSDS:-4.71, HVDS: -3.62), growth hormone secretion was evaluated. A severe GHD was detected (peak GH 1.56ng/ml in both tests) and rhGH therapy was initiated. MRI revealed ectopic posterior pituitary

Conclusion: We describe the case of a boy fulfilling criteria of CHARGE association (Blakes 1998, Verloes 2005) presenting with multiple anterior pituitary hormone deficiencies and structural pituitary abnormality. To our knowledge, this is the 3rd case in the literature where congenital hypopituitarism in CHARGE syndrome is associated with pituitary structural abnormalities and especially ectopic posterior pituitary.

P3-191

Hormone-secreting pituitary adenomas in children and adolescents

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Background: Hormone-secreting pituitary adenomas in children and adolescents are rare.

Methods: We report clinical course, management and outcome of 6 cases diagnoses in 2013-2019.

Results: Patients (3M, 3F), aged 9,5 – 16,5 years at referral. In them, 3 ACTH-secreting adenomas (ACTHA) and 3 prolactinomas (PROLA) were recognized. The family history for endocrine tumors was negative. In ACTHA, the patients' main complains were: growth retardation - 2, weight gain - 3, delay of puberty - 1, striae - 1, dysmenorrhoea - 1. The children with PROLA had headache - 3, primary amenorrhoea - 1, visual impairment - 3, delay of puberty - 1. Additionally, 1 girl with ACTHA had polymorphic skin rash after sun exposure and glucose intolerance. In one boy with ACTHA, the clinical course of previous asthma had been improved. The boy with PROLA had unilateral exophthalmus and tachycardia. Hypercortisolism was confirmed in 3 patients by a high FUC levels. On MRI, 1 ACTHA presented as macroadenoma (13*17*26mm); two were microadenomas. In one MRI-negative case, the diagnosis was confirmed only after separate catheterization of cavernous sinuses with ACTH secretion on the right 40 times higher than on the left. All 3 ACTHA were treated by transsphenoidal surgery with neuronavigation. After surgery, one boy had transitory and one has permanent secondary adrenal insufficiency; one girl has central hypothyroidism. There were two macroPROLA- and 1 giant PROLA. The prolactin initial levels were 2500- 138000 mU/l. Cabergoline was the first treatment in all patients. However, in the youngest girl PROLA was resistant to the weekly dose of 6 gr. and transsphenoidal surgery was done 2,5 years after conservative treatment with the normalization of prolactine level. Post-surgically, she is being treated with levothyroxine for central hypothyroidism. The giant PROLA in a boy was also TSH-secreting; somatostatin analogue was added to the treatment with PRL and TSH suppression and progression of puberty. In the oldest girl, partial surgical tumor resection was performed

Pituitary, Neuroendocrinology and Puberty

P3-190

Structural Pituitary Abnormality and Dysfunction Associated with Charge Syndrome

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Background: CHARGE is an autosomal-dominant syndrome which includes a variable combination of coloboma of the eye, heart malformations, atresia of the choanae, retardation of growth and development, and genital and ear abnormalities. CHARGE syndrome has rarely been associated with anterior pituitary dysfunction and with structural abnormalities of the pituitary gland only twice. We report the case of a child with CHARGE association and congenital hypopituitarism due to structural abnormalities of the pituitary gland.

Case Presentation: The patient was a boy born with IUGR (birth weight 2020gr, 37weeks' gestation). Clinical features included retinal coloboma and microphthalmia, choanal atresia, dysplastic auricles with small accessory auricle, multicystic dysplastic kidney and hypospadias with cryptorchidism. Endocrine testing revealed central hypothyroidism and secondary hypoadrenalinism. There was an inadequate response to low-dose intravenous Synacthen stimulation, with serum cortisol peaking at 10.3µg/dl at 1 hour. He was started on thyroxine and hydrocortisone replacement.

as emergency due to an acute visual impairment, with further rapid decrease of PRL. However, she continues treatment with cabergoline. In this case, gonadotropin's deficiency was detected, also elevated levels of GH and IGF-1 were found. The patient may need additional treatment with somatostatin analogue, as well as sex steroid replacement.

Conclusion: Pituitary adenomas, even those hormonally active, represent a challenge for diagnosis and follow-up in children and adolescents. A good collaboration between pediatric endocrinologists, neurosurgeons and other specialists of the team can improve clinical outcomes of such patients.

P3-192

Rohhad Syndrome: Report of 2 Rare Cases from Crete-Greece

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Introduction: ROHHAD syndrome (Rapid-onset Obesity with Hypoventilation, hypothalamic and autonomic dysregulation) is a rare and complex disease with potential fatal outcome. To this day there have been 158 cases reported in the literature while whole exome sequencing has not yet revealed any responsible genes. It usually presents at the age of 2-4 years and the diagnosis is based on the following criteria: 1) rapidly progressive obesity that develops at the age of 2-7 years 2) hypothalamic dysfunction 3) alveolar hypoventilation 4) dysregulation of the autonomic nervous system. In about 40% of the patients, neuroendocrine tumors have also been reported (ROHHAD-NET).

Aim: We hereby present, for the first time in Greece, two rare cases of ROHHAD syndrome from Crete.

Case Presentation: The first case, 20-year-old female, initially presented to the pediatric endocrinology outpatient care at the age of 9.5 with precocious puberty and obesity since the age of 4 years. On physical examination, her BMI was 27.6 kg/m², (>97th percentile), her height 1.46m and her bone age 12 years according to Greulich and Pyle. Pituitary MRI revealed a Rathke cyst without any other abnormal findings while laboratory testing showed hyperprolactinemia and low IGF-1. During follow up, the patient developed secondary amenorrhea, hypernatremia attributed to disrupted thirst mechanism, severe thermal dysregulation, hypothyroidism, while further testing with sleep study revealed obstructive sleep apnea, strongly suggesting ROHHAD syndrome. The second patient is a 16.5 year old boy who presented for the first time to the endocrinology outpatient care at the age of 14 years with significant obesity (BMI 38.08 >97th percentile) and metabolic syndrome. His height was 152cm (10th percentile) and his weight 88kg (>97th percentile) while he also demonstrated

delayed puberty (Tanner 2, testicular volume 6ml), acanthosis nigricans and multiple vertical reddish-purple skin striae. His bone age was compatible with his chronological age. Laboratory testing revealed hypernatremia, hyperprolactinemia, hypogonadotropic hypogonadism, growth hormone deficiency with normal cortisol secretion, insulin resistance, fatty liver disease, while sleep study demonstrated sleep apnea syndrome of increased severity for his age; findings compatible with ROHHAD syndrome. Currently, both patients receive hormonal replacement therapy while they also use a non invasive ventilation device (C-PAP).

Conclusion: ROHHAD syndrome is a rare disease which presents early in childhood. Rapidly progressive obesity and hypothalamic dysfunction are usually the first detectable signs of the disease. Prompt recognition of the syndrome as well as treatment of hormonal dysfunction and alveolar hypoventilation may prevent severe complications and increased morbidity mainly due to cardiopulmonary arrest.

P3-193

The Pubertal Development Mode of Chinese Turner Syndrome Girls with Hormone Replacement Therapy

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Background: Detail knowledge of pubertal development mode in girls with Turner syndrome (TS) who underwent hormone replacement therapy (HRT) is benefit for the proposal of an optimal HRT. The study was to study the pubertal development mode of girls with TS who underwent HRT and to evaluate the optimal therapy for sex induction in girls with TS. Method: We present a retrospective, longitudinal study over the past two decades from The First Affiliated Hospital of Sun Yat-sen University.

Patients: Clinical data from 71 TS patients and two groups of normal Chinese girls. Results: The total investigation time was 3.00(2.00, 4.66) yrs. The interval of each stage was significantly longer ($P < 0.001$) in the girls with TS than that in the normal Chinese girls except for Tanner stages B2-3 ($P = 0.011$). With the induction of estrogen, the uterine volume increased significantly when compared with the last stage (B3 vs. 2: $Z = -2.031$, $P = 0.042$; B4 vs. 3: $Z = -2.273$; $P = 0.023$; B5 vs. 4: $Z = -1.368$; $P = 0.171$). The uterine volumes of the girls with TS in stages B2, 3 were greater than those in the control group ($P = 0.046$), whereas the uterine volume of the control group was inversely greater than that of the TS group in those who reached stages B4 and 5 ($P = 0.034$). Paired data of 27 TS girls showed the uterine volume (17.93 ± 9.31 ml vs. 13.75 ± 6.67 ml) and width (2.54 ± 0.66 cm vs. 2.22 ± 0.36 cm) during artificial cycle increase significantly than that before ($t = -2.79$ and -2.51 , $P = 0.01$ and 0.018).

Conclusion: HRT leads to normal breast development in girls with TS, half of whom reached Tanner stage B5 in our study, although the uterus eventually developed a suboptimal status. The breast and uterus grew quickly at the beginning of HRT (stages B2-4). An optimal HRT regimen for girls with TS may specifically focus on Tanner stages B2-4 and artificial cycle.

Coincidental Central Precocious Puberty and Wilms Tumor

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Introduction: Wilms tumor is the most frequent pediatric renal malignancy and its usual presentation is an abdominal mass or hematuria. Unusual presentations have also been reported, such as paraneoplastic syndromes (acquired von Willebrand disease, sudden death due to pulmonary embolism and Cushing syndrome). These conditions can precede, occur concomitantly or present in a later phase of tumor development. Precocious puberty, as paraneoplastic endocrine syndrome, has already been described in children with malignant tumors (brain, gonadal, adrenal tumors and hepatoblastoma). However, little is known about central precocious puberty, as paraneoplastic manifestation of nephroblastoma or secondary to its specific chemotherapy.

Case Presentation: Here, we report a case of Wilms tumor and simultaneous precocious puberty in a 5-year-old girl. She presented with macroscopic hematuria and abdominal pain. Her personal and familial medical history were unremarkable. On physical examination a mass in the right upper quadrant was palpated. She had bilateral breast buds, corresponding to stage 2 of the Tanner classification and no other pubertal signs. The first diagnosis was nephroblastoma stage I and simultaneous premature telarche, confirmed by the pre pubertal levels of luteinizing (LH) and follicular stimulating hormone (FSH), and estradiol.

The oncological protocol was commenced, with complete excision of the tumor and chemotherapy cycles over 3 months.

A second endocrine assessment was performed at the end of chemotherapy. An accelerated linear growth (a gain of 3 cm in 4 months) and a rapid breast development (passage from stage 2 to stage 3) with no axillary or pubic hair were noted. The hormonal work-up found an activated pituitary-gonadal axis along with advanced skeletal maturation and ultrasound signs of uterine hormonal impregnation. The human chorionic gonadotropin (hCG) levels were normal. Brain magnetic resonance imaging showed a morphologically normal pituitary, but of pubertal size and no congenital or acquired lesions in the pineal or hypothalamic-optic region. The definitive diagnosis of idiopathic central precocious puberty (CPP) was made and the treatment with GnRH agonist was started.

Conclusion: An interesting point to consider is whether the CPP in our case represented a coincidental finding.

Collating data from the literature review relating to the proposed pathophysiological mechanisms underlying paraneoplastic syndrome and neoplasia-induced pubertal activation, and considering this alongside our patient's clinical evolution, we finally established that the association between Wilms tumor and CPP was purely coincidental.

Abstract withdrawn

Precocious pseudo-puberty presenting with bilateral ovarian involvement and progressing to juvenile granulosa cell tumor in a 2-year-old girl

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Background: Feminising precocious pseudo-puberty in McCune Albright syndrome (MAS) and juvenile granulosa cell tumour (JGCT) arises from bilateral and unilateral estradiol hypersecretion respectively. GNAS mutations have been described in some cases of JGCT as well causing MAS.

Aim: To describe a case in which MAS was evoked initially, but then progressed to JGCT

Case: A girl aged 2 years and 2 months, with no relevant family history, was admitted for premature sexual development. Her height was +2.6 SD, midparental height -0.4 SD, Tanner stage B3P2A1, bone age 5 yrs. Skin examination showed a single café au lait patch, 3cm in its largest axis, with irregular outline situated on the antero-lateral border of the left thigh. No other significant findings on examination were found including no bony lesion. LHRH test showed basal/peak LH 0.43/0.18 mUI/ml, FSH < 0.1 mUI/ml. Pelvic ultrasound showed an enlarged left ovary (63mm in longitudinal axis) and with multiple cysts (largest 38 mm). The right ovary was enlarged too (66mm in longitudinal axis) with multiple cysts (largest 38 mm).

MAS was considered likely and Tamoxifen 20 mg daily started. After only 7 weeks, there was a rapid increase in height and breast development to B3-4, with menorrhagia, bone age now 6.5 yrs. A second LHRH test showed gonadotrophin suppression. Pelvic ultrasound now showed a left-sided vascular solid/cystic ovarian tumour measuring 10x8x6 cm, with normal right ovary. Within a week, the tumour underwent torsion and was removed. The tumour weight was 850g, histopathology showed a juvenile granulosa cell tumour FIGO stage IA, mutational analysis for GNAS was negative.

Discussion: The aetiology in this case remains unclear, with MAS unproven, and evolution towards JGCT. Studies to determine AKT1 mutation in the tumour are planned. This case highlights current uncertainties in the causes of ovarian precocious pseudopuberty and the relationship between MAS and JGCT.

P3-197

Central precocious puberty in a boy with Prader-Willi syndrome during growth hormone replacement therapy

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Background: Prader-Willi syndrome is a genetic disorder characterized by obesity, short stature, hypotonia and hypogonadism. Delayed or incomplete puberty are usually found in PWS, whereas central precocious puberty is very rare.

Objective: This study aimed to report the case of a boy with PWS who was diagnosed with precocious puberty during growth hormone replacement therapy.

Methods: We retrospectively analyzed the genetics, clinical characteristics and laboratory findings of the boy.

Results: By the age of 4, the boy had mental retardation, epilepsy, characteristic face features, short stature with feeding difficulty in Neonate, and many clinical criteria of PWS diagnosis, which was confirmed by DNA methylation test (MS-MLPA). Therapy with recombinant human growth hormone (rhGH) replacement (0.1 IU/kg/day) was started. 2 years later, he performed increased testicular volume and growth velocity, high testosterone levels and advanced bone age. An ACTH test yielded a normal response and A GnRH test showed premature activation of the hypothalamic-pituitary-gonadal axis with pubertal gonadotropin and testosterone levels (gonadotropin-releasing hormone stimulated LH peak 20.51 IU/L, testosterone 3.32 nmol/L). Magnetic resonance imaging (MRI) of hypothalamic-pituitary region was normal.

Conclusions: In PWS, puberty is usually delayed and secondary sexual characteristics are almost always incomplete. True precocious puberty is very rare and only a few cases have been reported. Our patient fulfilled all diagnostic criteria for CPP. The rare manifestations of CPP in patients with PWS has been attributed to brain lesions. We hypothesize that our patient's precocious puberty resulted from abnormal brain discharge caused by epilepsy. Next step, we will treat the patient with gonadotropin-releasing hormone analog (GnRHa) and follow up his pubertal development.

P3-198

A Rare Cause of Hypogonadotropic Hypogonadism: FGFR1 Mutation

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Introduction: Mutations in *FGFR1*, which is involved in formation and migration of neurons responsible for the production of gonadotropin-releasing hormones, may either cause isolated hypogonadotropic hypogonadism (HH) or Kallmann syndrome

(KS). In addition, *FGFR1* mutations were reported in 2.7% of the cases with multiple pituitary hormone deficiency.

Case: A 16-year-old male was referred to our clinic with absence of pubic hair and micropenis. He had a history of surgery for bilateral undescended testes. He was adopted in neonatal period, his birth and family history could not be reached. His weight was at -2.62 SDS, height -2.72 SDS, BMI -1.12 SDS. He had flat nasal root, Tanner Stage 3 pubic hair, testicular volumes were 2 ml on the left, 0.5 ml on the right, and stretched penile length was 2 cm. Laboratory results were as follows: fT4 1.14 ng/dL (0.5-1.51 ng/dL), TSH 1.57 mIU/mL (0.38-5.33 mIU/mL), FSH 0.71 mIU/mL (1.3-19.3 mIU/mL), LH 0.08 mIU/mL (N>0.3 mIU/mL), total testosterone 0.49 ng/mL (2.59-8.16 ng/mL). Bone age was consistent with 13 years of age. Peak LH response during LHRH test was 4.75 IU/L (N, > 5 IU/L). Brain MRI was normal, no pituitary pathology was evident. There was no response to pubertal induction for two times, and low dose testosterone replacement was initiated. Growth velocity was low during the follow-up and insulin tolerance test showed low growth hormone (peak 1,36 ng/mL, N>7) and normal cortisol response to hypoglycemia. Whole exome analysis revealed a previously reported, heterozygous p.R622X mutation in *FGFR1*.

Conclusion: More than 25 genes have been identified to be associated with congenital HH. *FGFR1* mutations are among of the causes of congenital HH and KS, which are inherited autosomally dominantly and can be accompanied by cleft palate, tooth agenesis, and bimanual synkinesis. It should be kept in mind that multiple anterior pituitary hormone deficiencies may be associated with *FGFR1* mutations as well.

P3-199

Prolactinomas in a Pediatric Population

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Introduction: Prolactinoma is the most frequent pituitary tumor (40 %) in children and adolescents is more common in females, sporadic and benign. It is classified into microprolactinoma (< 1.0 cm) and macroprolactinoma (>1.0 cm). In girls it presents clinically as amenorrhea and galactorrhea and occasionally as increased intracranial pressure. Management consist of medications and surgery.

Objectives: To characterize patients seen at Pediatric Endocrinology Clinics from three Institution between July 2000 and November 2018.

Materials and Methods: Review of charts from patients with prolactinoma.

Results are presented in table 1. micro :microadenoma,Macro: macroadenoma *F:female.M:male, n/a does not apply

Pacient	age years	Sex	Galactorrhea	Amenorrhea	size	Prolactin. ng/ml	surgery	drugs
1	16	F	yes	yes	Macro	470	Si	Si
2	7	F	no	no	micro	500	No	Si
3	13	M	No	n/a	micro	651	No	Si
4	13	F	yes	yes	micro	67	Si	Si
5	15	F	yes	yes	macro	542	No	Si
6	14	M	No	n/a	micro	81	No	Si
7	15	M	No	n/a	macro	400	Si	Si
8	8	M	No	n/a	macro	1024	Si	Si
9	13	M	No	n/a	macro	470	No	Si
10	10	M	yes	n/a	macro	500	no	si

Analysis: Ten patients, mean age 12.4 ± 3.0 years, male 60%, 40% female, 60% debuted with galactorrhea, 75% of women with amenorrhea, 75% debuted with intracranial hypertension data 40% surgical management 60% had macroadenomas and 40% microadenomas, mean prolactin 470 ± 271 ng/ml.

Conclusions: We must suspect CNS tumors in patient with intracranial hypertension symptoms. Macroadenomas are more common in our pediatric population and as such surgery is the most common approach.

ceased due to non-compliance, was reintroduced at presentation. GH therapy was initiated at 19 years of age, resulting in 42 cm linear growth, to a final height of 124 cm. Sequencing of *POU1F1* revealed a previously described homozygous insertion mutation—c.580-581insT (p.Thr194llefs*7)—in exon 4 causing a frameshift that introduces a stop codon 7 amino acids forward, leading to a severely truncated protein lacking the homeodomain.

Conclusion: This case report sheds light on the natural history of untreated patients with *POU1F1* mutations and raises awareness for early diagnosis and adequate treatment of central congenital hypothyroidism and GH deficiency.

P3-200

Extreme Short Stature and Neurological Impairment in a 17-Year-Old Male with Untreated Combined Pituitary Hormone Deficiency Due to POU1F1 Mutation

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Introduction: POU1F1 is an essential transcription factor for the differentiation, proliferation and survival of somatotrophs, lactotrophs, and thyrotrophs. Mutations in the *POU1F1* gene are characterized by growth hormone (GH), thyrotropin and prolactin deficiencies, commonly presenting with growth retardation and central hypothyroidism. Since the first report in 1992, about 26 mutations have been identified in *POU1F1*.

Case Presentation: We describe a 17-year-old male who presented to our Pediatric Endocrinology clinic with extreme short stature (height 81.7 cm, -9.3 SD), cognitive impairment, deaf-mutism and neurological disabilities. L-thyroxine supplemental therapy, which had been initiated at the age of 6 months but

P3-201

The pituitary stem interruption syndrome: a neonatal pathology not to be ignored

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Introduction: Pituitary stem interruption syndrome (PSIS) is a congenital abnormality of the pituitary gland responsible for pituitary insufficiency. Its prevalence is unknown but about 1000 cases have been reported to date. It is characterized by a triad associating a very fine or interrupted pituitary stalk, an ectopic posthypophysis (PH) or absent and a hypoplasia of the anterior pituitary, visible on the MRI. The etiology of PSIS remains unknown.

Observation: We report the case of a newborn male, the first born of a couple consanguineous. Post-matured, born by high way with an average adaptation to the ectopic life. The diagnosis is revealed by the presence of hypoglycemia persistent, prolonged jaundice associated with a micro-penis and cryptorchidism suggestive of a hypothalamohypophyseal deficit. The karyotype was male 46 XY with no abnormalities detected. Hormonal exploration revealed a combined pituitary involvement: adrenal insufficiency, hypogonadism hypo-gonadotropic, central hypothyroidism with GH

deficiency. The hypothalamic-pituitary MRI showed hypoplasia of the anterior pituitary, a pituitary stalk interrupted with a PH in retro-chiasmatic.

Comment: Our patient had severe combined anterior pituitary deficiency, which explains the clinical picture. The diagnosis of PSIS is important from birth to avoid hypoglycaemia and adrenal insufficiency and their cerebral and vital risks. The prognosis is good if the diagnosis and treatment are early.

Conclusion: PSIS is a rare congenital malformation, responsible for isolated or multiple anterior pituitary deficiency. MRI is currently the most effective means of imaging for diagnosis and a prognostic approach. Treatment is based on substitution therapy for deficient hormones. The risk of family recurrence is less than or equal to 5%.

ICA. The oral glucose tolerance test showed impaired glucose tolerance. FOXA2 mutation was considered in the etiology and the result of genetic testing for FOXA2 is pending.

Conclusions: To date, seven cases from six unrelated families were reported to have FOXA2 mutations. All of these patients exhibited dysfunction in the glucose regulation and pituitary hormone deficiencies with varying degrees of gastrointestinal and vascular abnormalities. One patient with a complete deletion of FOXA2 gene presented with an interrupted inferior vena cava (IVC), midline liver, biliary atresia and malrotation but without hypopituitarism. Our patient had hypopituitarism, IGT, vascular and intestinal abnormalities. Also our case and one case in the literature has a phenotype that shows a transition from neonatal hypoglycemia to early childhood hyperglycemia. Our patient had dorsal pancreatic agenesis which has not been described previously. Further description of these cases will highlight to the development of the pituitary and pancreas.

P3-202

A Case Of Syndromic Hypopituitarism

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Objectives: Forkhead box A2 (Foxa2) is a transcription factor that plays a key role in foregut, pancreatic and central nervous system development. Here, we describe a 7 years old boy whose phenotype is consistent with FOXA2 defect.

Case: A 3 months old boy was referred for recurrent hypoglycemic events. He was born to unrelated parents at term with a birth weight of 3690 gr. At 6 hours of life he had severe hypoglycemia (venous glucose= 5mg/dl). Shortly after discharge, he was re-admitted to emergency department with cardiovascular collapse with an undetectable blood glucose level. Other biochemical measurements were consistent with hypopituitarism (cortisol: 3mcg/dl, growth hormone: 0.6 mcg/L, b-hydroxybutyrate 0.3 mmol/L, insulin 1.2 mU/L). Hydrocortisone and growth hormone replacement was initiated. He also had central hypothyroidism (TSH: 7mU/L (1.12-8.21); fT4:0.61 ng/dl (0.71-1.96)) and low prolactin levels (4.64 ng/ml). MRI of the pituitary gland revealed pituitary agenesis. On his initial examination height SDS was -1.19 (57cm), weight SDS was -1.56 (4.8kg). He was noted to have wide nasal bridge, bulbous nasal tip and smooth philtrum, bilateral cryptorchidism, micropenis and mild developmental delay. Abdominal ultrasonography revealed polysplenia. Abdominal MRI showed midline liver, situs inversus abdominalis, dorsal pancreatic agenesis, retroaortic left renal vein and inferior vena cava with azygos continuation. At two years old he was diagnosed with epilepsy and at 5 years with diabetes insipidus. At 5 years 8 months he developed postprandial glycemia and upper normal HbA1c (5.7%) with negative autoantibodies against GADA, IAA,

P3-203

Anaphylaxis Secondary to Gonadotrophin Releasing Hormone Agonist used for Precocious Puberty, Two Case Reports

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Gonadotrophin Releasing Hormone agonists (GnRHa) are used in the management of true precocious and early onset puberty. They have been associated rarely with severe adverse effects such as slipped capital femoral epiphysis, sterile abscess formation and anaphylaxis. Anaphylactic reactions had been reported at a low incidence rate. They can occur early or late after starting treatment or be recurrent after an injection due to the analogue's long half-life. The allergic reaction may be against the analogue itself or its vehicle, Polyacetic and Glycolic acids. Anaphylaxis to multiple analogues had been seen in the same patient.

Objective: To presents two cases that developed anaphylactic reactions after intramuscular Triptorelin Acetate depot injection, used to treat central precocious puberty. The first was a case of Mucopolysaccharidosis Type 3 and the second was a normal female with early accelerated puberty.

Method: The clinical information and lab results were obtained directly from the parents and the computerised medical records at the treating hospital.

Results: Case one presented with menstrual bleeding and secondary sexual characteristics at 6 years and 3months. She was started on Triptorelin Acetate and developed anaphylactic reaction after 2 hours of the first injection. Case two presented with signs of early puberty at 7years and 10 months, that accelerated rapidly. She was started on monthly Triptorelin Acetate at 8 yrs and 10 months. She developed anaphylaxis after the second injection. Both reactions required treatment in the emergency room with anti-allergy medication.

Conclusion: Although anaphylactic reactions are considered as rare adverse effects to GnRHa, they are presently seen more frequently as a result of the increased incidence of true precocious puberty and their more frequent use. Patient and parent education

of the anaphylaxis potential and associated symptoms is mandatory to prevent harmful consequences. Skin prick test is to be considered if the anaphylaxis incidence is seen to be increased.

Key words: Gonadotrophin releasing hormone agonists, central precocious puberty, drug related adverse effects, anaphylactic reactions.

P3-204**Central diabetes insipidus in children with pituitary stalk thickening in two cases**

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We present two cases of a 13-year-old boy and a 12-year-old girl who were initially diagnosed as central diabetes insipidus (CDI). The Magnetic resonance imaging (MRI) showed pituitary stalk thickening with prominent homogeneous contrast enhancement in T1W and the loss of high signal in the posterior pituitary. In addition to CDI, the two children have a common clinical manifestation of growth retardation, with the laboratory tests suggesting complete growth hormone deficiency. The girl presented sexual developmental delay with the laboratory tests suggesting hypogonadotropic hypogonadism, while the boy was in normal puberty sexual development, with the normal activation of the hypothalamic-pituitary-gonadal (HPG) axis. During the treatment of central diabetes insipidus with desmopressin acetate (DDAVP), the pituitary MRI of the boy and the girl suggested that the enlarged pituitary stalk progressed significantly after follow-up of 7 months and 5 months, respectively. After a multidisciplinary joint discussion, the surgery was performed by neurosurgery for biopsy, and the progressively thickened pituitary stalk of the 13-year-old boy and the 12-year-old girl were consequently confirmed to be Langerhans histiocytosis and germ cell tumor.

In these two cases of secondary CDI with pituitary stalk thickening, intracranial tumors and inflammatory diseases should be considered to be the first manifestations. Adequate assessment of endocrine, imaging, and clinical performance are extremely important. To those children, who were initially diagnosed as having idiopathic CDI with pituitary stalk thickening, especially accompanying with the signs of growth retardation, sexual developmental delay or hypothyroidism and so on, closely follow-up observation and appropriate time of pituitary stalk biopsy are necessary for the etiological diagnosis and therapy of the CDI with pituitary stalk thickening.

P3-205**Childhood craniopharyngioma: a single centre experience**

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Background: Craniopharingiomas are rare embryogenic malformations of the sellar and parasellar region with slow growth and high local recurrence rate. Due to their unfavorable location, pre-surgical hypothalamic involvement and treatment-related hypothalamic damage is frequent and lead to hypothalamic syndrome.

Objective: we compare weight gain and growth pattern regarding to hypothalamic involvement of pediatric patients affected by CF.

Materials and Method: we retrospectively review clinical data of 17 patients (8 female, 9 male) with childhood CF treated to our Centre. Median age of diagnosis was 8.1 ys with a median follow up time over 5 ys. Grading of hypothalamic involvement was based on neuroradiological and surgical assessment. Growth hormone replacement was started to all patients after 6-12 months from treatment.

Results: BMI SDS and HT SDS of 7/17 patients without hypothalamic involvement (41%):

	Diagnosis	Surgery	GH start	Puberty age	Last FU visit
SDS	-0,49	-0,30	-0,11	0,39	0,60
BMI					
SDS	-1,55	-1,96	-2,25	-1,55	-0,38
HT					

10/17 patients had hypothalamic involvement (59%):

	Diagnosis	Surgery	GH start	Puberty age	Last FU visit
SDS	0,59	1,44	1,95	1,76	2,53
BMI					
SDS	-0,84	-1,35	-1,49	-0,87	-0,02
HT					

Conclusions: Weight gain was significantly different between the two groups due to hypothalamic obesity. In the HY group weight gain was moreover rapid and progressive. Growth hormone treatment improved growth in all patients with height SDS within the normal limits at the last FU. Contrarily GH beneficial on weight appeared only temporarily.

P3-206

Unusual cause of hypopituitarism : A Niemann Pick Disease

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Introduction: Niemann Pick type B (NMP B) is a rare lysosomal storage disease caused by mutations in the SMPD1 gene. Typically, had normal height and weight. In this work, we report an unusual association of a Niemann Pick disease in a child with hypopituitarism.

Case: We report the case of a young boy who was hospitalized at the age of 11, in Hematological Department for splenomegaly and polyadenopathies where the diagnosis of Niemann Pick's disease was retained. At the age of 13 endocrine examination revealed pubertal delay with a Tanner stage: P1A1G1 and testis volume has been 2 mL, confirmed by a frankly low testosterone level 0.02 ng/ml contrasting with low gonadotropin levels: LH 1.5 UI/l and FSH 2.4 UI/l. Growth and development delay (Weight: 31 kg, Z score: -2.5 SD, height : 1.30 m, Z score -2.5 SD), Growth hormone was decreased after GH Stimulation Test, confirming GH deficiency, while IGF1 was within normal reference range, with integrity of other pituitary axes. Cerebral MRI showed an intra cranial arachnoidal cyst 8 × 14 × 30 mm of the posterior fossa. Pituitary gland and sella turcica were normal.

Conclusion: We conclude that a Niemann Pick disease could be associated with Growth and pubertal delay. Nevertheless, GH deficiency should be investigated.

P3-207

Precocious puberty and primary hypothyroidism in a 6 years and 10 months girl with pituitary macro adenoma and dextral ovarian cyst

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Background: Precocious puberty associated with profound hypothyroidism is a rare condition. It is usually characterized by breast development, vaginal bleeding, and lack of pubic hair. Multi cystic ovaries in profound hypothyroid patients with precocious puberty have been rarely described.

Case Presentation Summary: A 6 year and 10 month old girl was referred to Wahidin Hospital with precocious puberty. The girl was admitted with vaginal bleeding as the main complaint. Vaginal bleeding occurred since 6 months before with 3-4 days cycle. Breast enlargement and hairy axillary since a year before. Her mother had menarche at 14 years old. There was consanguinity of her both parents. On physical examination: pigmented hairy axillary, breast budding, no pubic hair. Body weight 20 kg, height

108 cm. Genetic height potential 142,5 cm - 159,5 cm (CDC NCHS 2000). Laboratory: hemoglobin 8,4 g/dl, perifer blood smear dysmorphyc anemia from Fe deficiency with differential diagnosis chronic illness. Low LH but FSH and estradiol elevated. Low FT4, T3 (total) and T4 (total) with high TSH and prolactin. Tumor marker : AFP, CEA and Beta HCG normal with light elevation in Ca-125. MSCT abdominal scan ovarian cystic. Bone age for left hand appropriate with 6 years and 10 months girl. Head CT scan suggestive pituitary macro adenoma, bilateral fronto temporal hypoplasia. This patient treated with levothyroxin 100 mcg/24 jam/oral.

Discussion: Precocious puberty associated with profound hypothyroidism is a rare condition and can be treated with levothyroxine which can give tumor reduction and stop bleeding.

Keywords: Precocious puberty, hypothyroidism, pituitary macro adenoma, levothyroxine

P3-208

The early predictors of serum IGF-1, DHEAS, AMH and BMP-6 in rapidly progressive puberty girls

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Objective: To investigate the early predictors of serum IGF-1, DHEAS, AMH and BMP-6 in rapidly progressive puberty girls.

Methods: 750 cases of central precocious puberty (CPP), early puberty (EP) and rapidly progressive puberty (RPP) in Children's hospital of Soochow university were recruited from August 2017 to December 2018. After follow-up six months to one year, 138 girls were divided into CPP (n=32), EP (n=65) and RPP (n=41). Healthy control group is 33 normal physical examination girls, whose age is 8~9 year old.

All cases were divided into five groups: CPP group, EP-RPP group (early puberty with rapidly progressive group), EP-SPP group (early puberty with slowly progressive group), RPP group (rapidly progressive puberty group) and healthy control group, serum, detail medical history, parent's heights and auxiliary examinations were collected.

Test the serum concentrations of IGF-1 and DHEAS by Chemical Luminescence, test the serum AMH and BMP-6 by Enzyme-linked immunosorbent assay.

The statistical analysis software was SPSS22.0.

Results and Conclusions: The peak value of serum FSH and peak ratio of serum FSH/LH in EP-SPP group is higher than those in EP-RPP group, and there is no significant difference of the peak value of serum FSH between EP-RPP and RPP, indicated that the peak value of serum FSH combine with the peak ratio of serum FSH/LH may be used as the one of the early predictors for RPP.

The value of serum IGF-1 was higher in EP-RPP group than in EP-SPP group, with the puberty rapidly progressed, the value of serum IGF-1 was gradually increased, indicated that IGF-1 was related to the progress of puberty, and may be used as the one of the early predictors for RPP. The optimal cut-off value was 232.5ng/ml, which specificity and sensitivity was 79.00% and 69.00% respectively. Additionally, the value of serum IGF-1 was higher in

EP-RPP group, EP-SPP group and CPP group than those in healthy control group, meant that IGF-1 was involved in the initiation of puberty.

DHEAS cannot be used as an early predictors for RPP, it may be related to Tanner staging.

The value of serum AMH and BMP-6 in EP-RPP group, EP-SPP group, RPP group, CPP group and healthy control group were no significant difference.

early menarche and short stage will also happens in early puberty girls, it is important to observe the progression of puberty.

P3-209

Pituitary hyperplasia as a complication of severe hypothyroidism due to Hashimoto's thyroiditis could impair pituitary function

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Introduction: Long-standing primary hypothyroidism is an unusual cause of pituitary hyperplasia (PH) in children, sometimes difficult to distinguish on CT or MRI from primary pituitary tumors. Loss of thyroxine feedback determines overproduction of thyrotropin releasing hormone (TRH) and subsequent TSH-releasing cells hyperplasia in the anterior pituitary. Levothyroxine replacement therapy has been shown to usually determine regression of PH.

We report the case of 11-years-old girl with PH in which growth arrest was the only symptom of a severe primary hypothyroidism due to Hashimoto's thyroiditis (HT).

Case Report: A 11-years-old, Caucasian, prepubertal girl referred to Outpatient Clinic because of complete statural growth arrest in the last year as unique clinical feature. To exclude the intracranial expansive pathology, brain MRI was immediately performed and revealed anterior pituitary enlargement (pituitary volume 648.9 mm³). Hormonal evaluation documented: markedly elevated TSH (319 µUI/ml) and very low FT4 (2.79 pmol/L) associated with positive antibodies to thyroglobulin and thyroid peroxidase (289 UI/ml and 4580 UI/ml, respectively), suggesting HT also confirmed by thyroid ultrasound (normal thyroid volume, diffuse hypoechogenicity and increased parenchymal vascularization). Other basal hormonal evaluation demonstrated slight hyperprolactinemia (497 mUI/ml, normal range 102-496) and low concentrations of cortisol (5.3 pg/ml, 7.3-32), IGF-1 (88.5 ng/ml; 146-462) with subnormal GH secretion (GH peaks 6 ng/ml and 7 ng/ml in clonidine and glucagon stimulation tests, respectively). Gonadotropins (FSH 2.15 mUI/ml, LH <0.3 mUI/ml) and estradiol (< 5 pg/ml) were in prepubertal range. Screening for celiac disease was negative. Levothyroxine treatment (2 mcg/kg/day) was immediately started.

Six month after the beginning of levothyroxine, patient presented increased growth velocity (4.4 cm, 0.42 SD), onset of puberty (Tanner stage B2), normalization of thyroid (TSH 0.60 µUI/ml, FT4 18.7 pmol/L) and pituitary function (cortisol 11.87 ug/ml, IGF-1 182.8 ng/ml, GH peak 10.52 ng/ml, prolactin 88.6 uUI/ml, estradiol 42.30 pg/ml, FSH 4.01 mUI/ml, LH 0.88 mUI/ml). PH regression was also documented by MRI (218.4 mm³).

Conclusions: PH due to primary hypothyroidism should be considered in the differential diagnosis of statural growth arrest. PH may cause temporary deficit of the pituitary tropins secretion, in particular, GH secretion impairment might be due to TRH-induced transdifferentiation of somatotroph into thyrotroph cells, as previously demonstrated in murine model.

In patients with pituitary enlargement, thyroid function tests are important to recognize PH secondary to primary hypothyroidism so as to avoid unnecessary surgery.

P3-210

Homozygosity for Proopiomelanocortin (POMC) mutation in a Palestinian child

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Background: Congenital Proopiomelanocortin deficiency (POMC) is a rare autosomal recessive disorder characterized by the association of adrenal insufficiency, early onset obesity, hyperphagia and altered skin & hair pigmentation. POMC is a complex propeptide encoding a range of melanocortin peptides that are released by tissue-specific proteolytic processing. These peptides have important roles in a range of functions such as skin pigmentation and the control of adrenal growth and function. In the central nervous system, POMC is most highly expressed in the arcuate nucleus of the hypothalamus, and POMC-expressing neurons are critically involved in the control of appetite and energy balance.

Here we describe a novel homozygosity mutation for POMC gene in a Palestinian family with congenital proopiomelanocortin deficiency.

Clinical Data: A Palestinian infant, born to consanguineous parents, presented with early onset obesity, hyperphagia, adrenal insufficiency, and red hair. Cortisol level was undetectable before and after stimulation, very low ACTH level. Congenital Proopiomelanocortin deficiency syndrome was suspected and confirmed by molecular testing.

Molecular Data: DNA sequencing of the POMC gene revealed a homozygous mutation c.296delG (p.G99AfsX59) in exon 3, while his father & mother are heterozygous. This mutation has been detected before as a compound heterozygous and as a disease causing mutation.

Conclusion: To our knowledge, this is the first description of this disease in a Palestinian family with molecular confirmation in a homozygous form, allowing accurate genetic counseling, early diagnosis of affected kindreds, early therapeutic interventions and avoiding complications.

P3-211

Peculiarities of Clinical Options for Delaying Sexual Aging In Boys-Adolescents

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Delayed puberty (DP) in boys is considered the most common hypoandrogenia of puberty. It should be noted that DP adversely affects physical development, body formation and the health status of adolescents. The heterogeneity of the population of adolescents with DP has led to a differentiated approach and the allocation of the following three clinical options (CO) of DP: 1 - DP, accompanied by growth retardation; 2 - DP without significant deviations in physical development; 3 - DP, accompanied by overweight.

Aim of Research: to study the clinical and hormonal features of clinical variants of DP in boys.

Materials and Methods: 52 adolescent boys aged 13–18 years old with DP were examined. Evaluated height, SDS height, body mass (BM), with the calculation of body mass index (BMI). The lack of ossification (LO) was established as the difference between the passport and bone age, as determined by X-ray examination of the bones of the right hand. The method of enzyme immunoassay studied the levels of luteinizing (LH) and follicle-stimulating (FSH), sex (estradiol (E2) and testosterone (T)) hormones, which were evaluated taking into account the age group (13-14, 15-16, 17-18 years).

Results: The most frequent first CO DP (46.2%), in which adolescents had growth deficit (-2.68 SDS), expressed as LO (-3.27 years). The second CO DP was observed in 36.5% of the examined, while the SDS height was (-1.34) and there was a pronounced LO (-3.26 years). The third CO DP was detected in 17.3% of boys, the SDS height was (-0.38), significant LO (-2.83 years). All adolescents with DP, regardless of CO, had significant deviations of the hormonal status. The average content of LH and FSH in all age groups was significantly lower than the normative ($p < 0.05$), which indicates a violation of gonadotropin function in all examined, most pronounced in patients 13-14 years old with 3 CO and 17-18 years old with 1 and 2 CO. The majority of the examined patients showed low functional activity of the testicles (reduced T content), most pronounced at 3 CO, as well as among young men of 17-18 years old at 1 and 2 CO. At 3 CO, a regular increase in the level of E2 was noted against the background of excess adipose tissue.

Auxology

Age (years)	2.2	4.4	5.7	6.3	6.8	7.3	7.5	8.7	9.5	10.2
Ht SDS	-2.21	-2.05	-2.01	-1.75	-1.76	-1.49	-1.32	-0.34	-0.47	-0.38
BMI SDS	-3.32	-1.67	-0.75	-0.66	-0.52	-0.5	-0.42	+0.49	+0.94	+0.45

Conclusion: The identified clinical and hormonal peculiarities in case of various CO of the DP will help in choosing the optimal treatment tactics and monitoring of such adolescents.

P3-212

Two separate pathologies (Coeliac disease and Central precocious puberty) associated with catch-up growth in the case of a child born small for gestational age (SGA)

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Case: MMW was born at 39 weeks by elective caesarian section because of placenta praevia with a birth weight of 2.32kg. She was known to dietetics and medical services because of failure to thrive and short stature (BMI SDS -3.32, Height SDS -2.21). Due to chronic upper airways obstruction, she had a tonsillectomy at aged 2.5 yrs. Following this, appetite and weight improved (BMI SDS -1.3) but abdominal pains prompted blood investigations which revealed positive coeliac serology (tTg and endomyseal antibodies). Diagnosis was made by HLA typing at 6.3 years by a Paediatric gastroenterologist. She was discharged to general follow up when growth improved on a gluten free diet at 7.3 years. Catch up growth was presumed to be due to her medical management. However she presented in B2 puberty 3 months later at 7.5 years. Bone age advancement was noted and LHRH stimulation test confirmed a central cause for her precocious puberty (LH peak 14.72 IU/L, oestradiol 121 pmol/L). GNRH analogue was started a few weeks later (7.6 years).

Imaging: Bone age 3 yrs (CA 5.7 yrs). Bone age 5 yrs 9 months (CA 7.5 yrs). Bone age 10 years (CA 9.1 yrs). Pituitary MRI was normal.

Conclusion: Typical bone age delay is seen in a child with chronic feeding difficulties and obstructive airways. This bone age delay is noted to advance when she presents with precocious puberty at 7.5 years. One can assume the trigger for earlier puberty here may be due to improved nutrition and BMI following improved appetite following tonsillectomy and being gluten-free after coeliac diagnosis. However the natural progression of catch-up growth in a SGA child may also be influencing growth patterns and bone age advancement here.

P3-213

Mitochondrial Encephalomyopathy with Acidosis and Stroke-Like Episodes in A Vietnamese Child: Clinical, Radiological And Molecular Genetic Analysis

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Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) is a mitochondrial multisystem disorder. The m.3243A>G pathogenic variant in the mitochondrial gene *MT-TL1* is present in approximately 80% of individuals with MELAS. In this article, we report a 7-year-old girl with the classical MELAS phenotype. After the age of 1 year, she had recurrent episodes of nausea and vomiting. In this episode, she presented with focal seizures in the left side. Examination showed generalized muscle weakness and mild left-sided hemiparesis. Blood and cerebrospinal fluid lactate elevated 6.2 mmol/L (normal range 1.8-2.7) and 8.5 mmol/L (normal range 1.2-2.1), respectively. The brain magnetic resonance imaging (MRI) revealed infarct-like lesions in the right prefrontal, temporal and occipital regions. The heteroplasmic A3243G mutation was detected in the blood of the patient by using Polymerase Chain Reaction-Restriction Fragment Length Polymorphism analysis and direct sequencing in the system of ABI 3500 Genetic Analyzer. A daily dose of 200 mg/kg/day oral arginine was given. Treatment for MELAS is primarily supportive. Patients should be followed at regular intervals to monitor progression and the appearance of new symptoms.

neurogenic causes. When confronted with a very young child with sexual precocity, full endocrine work up is necessary and there is no doubt for the need to treat.

Case: SG presented at the age of 2.6 years with thelarche and pubarche for one month. As her mother is tall (175cm, 97th centile), she was concerned that her child had grown more rapidly in the last 7 months. There was no significant family history. Birth weight was 2.745 kg following elective caesarian section at 38 weeks gestation for pre-eclampsia. Growth tracked along the 25th centile for weight in the first year, and 91st centile for height. On examination, she was in A1 B2 P2. Treatment with GnRH analogue as Triptorelin was started within days of her blood test results. She tolerated her induction treatment with close monitoring of height velocity clinical symptoms. Decapeptyl was administered at short intervals of 8 weekly due to a detectable LH. She appeared happier with less temper tantrums and has stayed at B2.

Endocrine profile:

2014

	Time 0	Time 20 min	Time 60 min
LH (IU/L)	2.65	113.91	77.47
FSH (IU/L)	4.12	18.84	18.64
17B oestradiol (pmol/L)	<73		

Prolactin 156 mU/L (0-566) TSH 1.63 mU/L (0.3-5.6) 17OHP 2 nmol/L androstenedione 1.9 nmol/L DHEA-S 0.5 umol/L testosterone <0.35 nmol/L IGF1 36.5 nmol/L (2.1 - 23.1). Tumour markers (bHCG, AFP) were negative. Urine steroid profile normal. Karyotype 46 XX.

2016

LH 0.8 U/L FSH 1.8 U/L

2018

LHRH stimulation test at 8th week - LH peak 1.83 U/L, FSH 1.76 U/L, 17B oestradiol < 73 pmol/L.

Imaging: Bone age 6 yrs 10 mths (CA 2.6 yrs). Pituitary MRI normal. Pelvic ultrasound - tiny ovarian follicles bilateral (0.6, 0.7 ml volumes), uterus 36x12x21 mm, 1.2mm endometrium. BA 7 yrs 10 mths (CA 5.6 yrs), 10 yrs (CA 7 yrs).

Conclusion: Growth remains rapid in this child with a tall mother. It is unusual to see a case so young with no neurogenic cause for her central precocious puberty.

P3-214

Central precocious puberty in a 2 year-old with no sinister cause

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Background: The causes of most cases in girls with central precocious puberty is idiopathic, and tend to be older compared with

Auxology

	2014	2015	2016	2017	2018	2019
Height cm (Ht SDS)	104.7 (+3.84)	109.9 (+3.7)	119.8(+3.34)	126.4(+3.13)	131.3 (+2.94)	134.4 (+2.92)
Weight kg (BMI SDS)	17.6 (-0.04)	19.3 (+0.07)	21.7 (-0.28)	24.5 (-0.07)	26.2 (-0.21)	29.1 (+0.27)

P3-215

MKRN3 Gene Mutation in a Case of Familial Central Precocious Puberty

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Introduction: Gain-of-function mutations in *KISS1* and *KISS1R* genes and loss-of-function mutations in the gene encoding the *makorin RING-finger protein 3 (MKRN3)* expressed only in the paternal allele are the most common genetic reasons of familial central precocious puberty (CPP).

Aim: We report a case of familial CPP and a pathogen variant in the *MKRN3* gene.

Case: The girl who was 7 years and 4 months old with breast and pubic hair development of three months duration referred to pediatric endocrinology clinic. Medical history was usual and her parents were unrelated. Her father, paternal uncle and cousins had a history of CPP although without documentation. At the time of first visit; weight was 34 kg (2.06 SD), height 127 cm (0.78 SD), BMI at 97 centiles, with a target height of 148.1 cm (-2.01 SD, mother height -1.52 SD, father height -3.44 SD), breast Tanner stage II, pubic hair Tanner stage II. On physical examination, no other abnormalities were observed. Laboratory findings; FSH: 4.1 IU/L (N: 0.1-4.3), LH: 0.8 mIU/mL (N: <0.1), E2:17 pg/mL (N: <12), and thyroid function tests and routine blood studies were normal. Bone age according to Greulich-Pyle was 10.5 years. On pelvic ultrasound, uterine length was determined 50 mm, left ovary 3.3 ml and right ovary 3.3 ml. GnRH stimulation test was performed and it was indicative of CPP. Magnetic resonance imaging (MRI) of the hypothalamic-pituitary region revealed normal findings. Considering the family medical history of father side, we suspected a genetic cause for the CPP, and therefore, we focused on MKRN3. MKRN3 gene analysis showed a previously identified c.482dupC heterozygous variant in the patient and her father. The variant caused premature stop codon as a result of frameshift and therefore was thought to be pathogenic. Treatment with Gonadotropin-releasing hormone analog was started (3.75 mg of depot leuprolide acetate, every 4 weeks). She is 9 years and 3 months old now, and weight 47 kg (2.25 SD), height 139.5 cm (0.55 SD). Bone age is 12 years and breast and pubic hair are Tanner stage III. Clinical follow-up is continued with GnRH analog treatment.

Conclusion: In the evaluation of CPP cases, family history and genetic analysis are important in terms of early diagnosis and treatment with genetic counseling of the next generations.

P3-216

Family Central Early Puberty about Three Sisters

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Introduction: Early puberty is defined in the girl by the appearance of secondary sexual characteristics before the age of 8 years. Unlike the boy, the central origin is most often idiopathic. The familial nature encourages looking for a genetic mutation which can explain this early maturation of the gonadotropic axis.

Cases: These are three girls from a consanguineous marriage. They had no particular pathological antecedents, including no similar cases in the family. The reason for consultation was an isolated breast development with a tanner stage was S3P1A1 in the three girls. And the average age of discovery was 5 years 3 months; the clinical examination was normal except a statural advance estimated at +2 SD to +3SD with normal bone age. Hormonal exploration showed an average rate of estradiol at 16 pg /ml with extremes (8-25), FSH at 3.43 mUi/ml with extremes (2.3-4.4) and LH level at 0.63 mUi/ml with extremes (0.28-1.1). Pelvic ultrasound had objectified an enlarged uterus (40mm * 18mm * 14mm) with multiple follicular ovaries. Hypothalamic-pituitary MRI eliminated an organic cause. The central idiopathic origin of precocious puberty was therefore retained and the three girls were put on GnRH analogues with a good evolution and stability of their pubertal state.

Conclusion: Certainly the progress of molecular biology will be of great contribution to the understanding of the phenotypic variability as well as the atypical aspects of early puberty and especially in family cases as illustrated by our observation.

Sex Differentiation, Gonads and Gynaecology or Sex Endocrinology

P3-217

Clinical and Molecular Spectrum of Patients with Disorders of Sex Development: A Single Center Experience

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Introduction: Disorders of sex development (DSD) constitute a group of congenital conditions that affect urogenital differentiation and are associated with chromosomal, gonadal and phenotypic sex abnormalities.

Objective: To evaluate clinical and genetic features of childhood DSD cases.

Materials and Methods: DSD patients followed up between the years of 1981-2018 were evaluated in terms of their complaints, demographic, clinical features and genetic diagnoses.

Results: Out of 250 patients, 136(54%) were classified as 46, XY DSD, 59(%24) as 46, XX DSD and 54(22%) as sex chromosomal DSD. The median age at admission was 5,2(0-19) years. Molecular diagnoses was made in 121 of the patients (48%). The distribution of the molecular diagnosis of the 47(34,5%) 46 XY DSD patients were; 13(27%) SRD5A2, 7(14%) HSD17B3, 6(13%) AR, 3(6,3%) AMHR2, 2(4,2%) LHCGR, 2(4,2%) WT-1, 2(4,2%) HSD3B2, 2(4,2%) CYP17A1, 1(2,1%) SRY, 1(2,1%) AMH and 1(2,1%) DHCR7. One patient had Y microdeletion. Two new suspected genes were detected by whole exome sequence analysis, which could be associated with ambiguous genitalia. One of them is homozygote c.332delC mutation in CCDC60 gene. The other is homozygote c.36_41dupGGAGGC mutation in ZNF653 gene. Forty nine of the 46, XX DSD patients were diagnosed with clinical and laboratory findings. 24(%40,6) of them was 21-hydroxylase deficiency, 9(15,2%) Mayer-Rokitansky-Küster-Hauser syndrome, 4(6,7%) 11-β hydroxylase deficiency, 4(6,7%) gonadal dysgenesis, 2(3,4%) aromatase deficiency, 2(3,4%) uterus anomaly, 1(1,7%) cloacal anomaly, 1(1,7%) vaginal agenesis, 1(1,7%) pregnancy related luteoma and 1(1,7%) ovotesticular DSD. In 46, XX group pathogenic mutations was detected in 20(33,8%) of the patients. Of these 16(80%) was CYP21A2, 1(5%) CYP11B1, 2(10%) CYP19A1 gene mutations and 1(5%) was SRY+ gonadal dysgenesis. Fifty-five (24%) of the patients were diagnosed as sex chromosomal

disorder. Of these 39(72,2%) were Turner Syndrome, 3(5,5%) Klinefelter Syndrome, 10(18,5%) mix gonadal dysgenesis, 1(1,8%) 47 XXX and 1(1,8%) 47 XYY. All of the patients who decided gender change chose chromosomal sex (2 patients 46, XX, 8 patients 46, XY). 3(30%) of them was 5α-reductase deficiency, 1(10%) 17 β hydroxysteroid dehydrogenase-3 deficiency, 1(10%) 21-α hydroxylase deficiency and 1(10%) 3-β hydroxysteroid dehydrogenase deficiency. Malignant and pre-invasive gonadal malignancy were diagnosed in 8 patients.

Conclusion: Etiology of many DSDs are still cannot be established and they are arising due to complex genetic mechanisms.

P3-218

Clinical observation of oral testosterone undecanoate treatment for children with 5-alpha-reductase deficiency

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Objective: Clinical Observation of fifty-two patients with 5-alpha-reductase deficiency (5 - alpha-reductase deficiency, 5α-RD) with oral testosterone undecanoate. To evaluate the efficacy and drug safety, find the optimum age of medication.

Methods: Prospective self-controlled comparison methods were used to analyze the clinical data and follow-up results in sixty-nine patients who are diagnosed with 5-alpha-reductase deficiency by ** hospital with continuous oral testosterone undecanoate capsules (2~3 mg/Kg/day, maximum dose of 80 mg/day) from March 2009 to April 2018.

Results: Sixty-nine patients with 5-alpha-reductase deficiency were included in the study, ranging in age from 0.1 to 8 years old, with an average age of (2.2±1.7) years old. The clinical manifestations were small penis with different degrees of hypospadias and 4 cases of pure small penis. A total of 68 cases were treated with oral testosterone undecanoate capsules (PL>2.5SD). The effective rate of the first course of treatment was 47.92%, the effective rate of the second course was 91.67%, and the optimal length of penis was reached in the second course. The length of growth of the penis in the first course was (0.83 + 0.47) cm, the length in the second course was (0.60 + 0.35) cm, and the final length was about (3.09 + 0.53) cm. The efficacy of undecanted testosterone before puberty was significant in these patients, and the fitting curve analysis showed that there was no correlation between the efficacy of drug and age before puberty (R^2 was far less than 1), and there was no significant difference in the efficacy among all age groups ($P>0.05$). The height, weight, BMI, bone age and sex hormone levels of the patients were regularly monitored without affecting the physical growth and development of the patients. Two patients were followed up to 18 years old, and there was no significant difference between the DSD of final height and expected target height.

Conclusion: Theseageof 5-alpha-reductase deficiency patients was stratified. Their clinical manifestations was almost small penis with different degrees of hypospadias. The effective rate of oral undecanted testosterone was 91.67%, and the effect of the first course was better than that of the second course before puberty. There was no correlation between drug efficacy and age in prepubertal. The drug's short-term safety was relatively high and had less effect on bone age and target height with these patients.

P3-219

Final adult height in SRY-negative 46, XX ovotesticular differences of sex development individuals

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Introduction: Differences of sex development (DSD) encompass a variety of conditions with atypical development of chromosomal, gonadal or anatomic sex. 46, XX ovotesticular (OT) DSD is a rare condition, in which the presence of testicular and ovarian tissues is identified in the same individual. These patients present variable phenotypes with a wide spectrum of atypical genitalia and their sex assignment can be male or female. Short stature is a frequent issue in patients raised in the male sex.

Objective: To describe the final adult height of ten 46,XX OT patients untreated with recombinant human growth hormone (rhGH) and two 46,XX OT patients treated with rhGH.

Methods: The final adult height of twelve male SRY (-) 46,XX OT-DSD patients were retrospectively studied. Two of them (cases A and B) received 0.05 mg/Kg/day rhGH therapy, associated with GnRH analog or aromatase inhibitor. Ten patients not received rhGH therapy neither hormone-blocking therapy. Seven of 10 patients had spontaneous puberty and in three patients that underwent bilateral gonadectomy at childhood, pubertal induction was done.

Results: Mean adult height in 46,XX OT DSD patients that not received rhGH therapy was 163.7cm (range: 153.5 to 176cm). The final adult height in patients with spontaneous puberty was 163,5cm and in the induced puberty group was 165,8cm.

Case A: Therapy with rhGH was started with chronological age (CA) of 10 yrs and bone age (BA) of 13 yrs. His height was 136cm (SD -0.3) and the growth rate (GR) 3.5cm/year. The target height (male sex) was 169cm. GnRH analogue was simultaneously initiated and was maintained for 9 months. The duration of rhGH therapy was 5 yrs. His adult height was 171cm.

Case B: Pubertal induction using testosterone esters (50mg, monthly) was started at 14 yrs-old, BA was 13.5 yrs, GR 5.2cm/yr and height 141cm. The rhGH treatment was started at age of

15.1 yrs, BA 14 yrs and height 147cm (SD -2). Throughout the first year of rhGH, his GR was 9.4 cm. Letrozole (2.5 mg daily) was associated in the last 6 months of treatment. The duration of rhGH therapy was 1.75 yrs. His adult height was 158.5cm. He was adopted and the informed target height (male sex) was 152cm. Side effects were not observed in the both patients.

Conclusion: Early rhGH treatment may be useful to optimize growth and the adult height of male raised 46, XX ovotesticular DSD patients.

P3-220

A rare cause of SRY (-) 46, XX DSD: Aromatase deficiency

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Introduction: Aromatase deficiency is a rare cause of autosomal recessive 46, XX disorders of sex development (DSD) due to *CYP19A1* gene mutations. The affected patients cannot have a normal estrogen biosynthesis. It is characterized by low serum estrogen, increased gonadotropins, and ovarian cysts. Herein, we report a new case with aromatase deficiency.

Case Report: A 1-month-old girl was referred due to cliteromegaly. Her mother developed acne, voice change and hirsutism during pregnancy. She was born with a birthweight of 2990 gr at the 37th week of gestation. The parents were nonconsanguineous. The physical examination was unremarkable except a cliteromegaly of 1.3 cm and posteriorly fused labia minora. Initial evaluations excluded virilizing congenital adrenal hyperplasia. In hormonal analyzes (Table-1), FSH, LH and testosterone levels were high and E2 level was very low. Pelvic ultrasonography revealed a normal uterus and multiple ovarian cysts. Karyotype was 46, XX and SRY was negative. Aromatase deficiency was considered due to the presence of maternal virilization, detection of hypergonadotropic hypogonadism during mini-puberty and low estradiol levels despite elevated total testosterone levels. A previously identified homozygote mutation in *CYP19A1* (c.628G>A, p.Glu210Lys) was found. During the follow-up, the fusion at the posterior of the labium minus was surgically corrected.

Conclusions: Aromatase deficiency should be kept in mind in patients with SRY (-) 46,XX DSD cases particularly whenever there is a history of maternal virilization during pregnancy.

Table-1

	28 days	3 months	6 months
FSH (mIU/ml)	72,3	83,2	77,5
LH (mIU/ml)	34,8	9,1	20,7
E2 (pg/ml)	<5	<5	<5
Total Testosteron (ng/dl)	107	<20	109
17-OH Progesterone (ng/ml)	3,8		
ACTH (pg/ml)	44,56		
Cortisol (mcg/dl)	8,83		

P3-221**Gonadal dysgenesis, 46 XY about 5 familial cases**

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Introduction: Sexual disorders 46 XY are responsible for a range of phenotypic disorders; from an ambiguous phenotype to a complete female phenotype. This is often a sporadic condition. In this context, we report 5 cases of gonadal dysgenesis, 46 XY belonging to the same family and particular phenotypic expression. this particular phenotype arise a question about the link between familial sexual differentiation disorders and the panel of genes involved in sexual differentiation.

Results: We report 5 patients borned from a consanguineous marriage, presenting for a micropenis with bilateral cryptorchidis. The average age at diagnosis was 30.5 years(extreme:17-37). On examination, the phenotype was male without dysmorphia in all cases, with a penis size ranging from 1 to 2 cm (-3SD). A gynomas-tia (S5) was present in 4 cases, with palpable gonads at the inguinal level. Pelvic ultrasound confirmed the presence of two gonads in the inguinal position. The karyotype had shown a homogenous chromosomal formula compatible with a male genetic sex,type 46,XY. Hormonal exploration confirmed a low testosterone levels with an average at 0.02 ng/ml, and contrasting with high levels of gonadotropins : FSH, an average of 81 mUI/ml (extremes:55-110); LH level at average of 29 mUI/ml (extremes:9-47). The AMH assay and the biomolecular study of the genes involved in testicular differentiation are currently being carried out.

Conclusion: Sexual differentiation anomalies cover a broad spectrum of phenotypic and genotypic anomalies in a particular cohort because of the occurrence of gonadal dysgenesis picture in 5 members of the same family, and certainly involving one or more genes involved in the sexual differentiation cascade. Admittedly, advances in molecular biology will make a major contribution to the understanding of phenotypic variability as well as the atypical aspects of gonadal dysgenesis.

P3-222**Research on Detecting the Dose of Estrogen in the Hormone Replacement Treatment in Girls with TS – A Retrospective Study in Single Clinical Center**

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Objective: The study was to detect the proper regimen of estrogen in HRT in girls with TS.

Method: We conducted a retrospective, longitudinal study with 76 girls with TS from The First Affiliated Hospital of Sun Yat-sen University over the past two decades.

Results: The investigation time was 3.00 (2.00, 4.66) yrs. The uterine volume grew significantly till B4 stage when compared with last stage (Z_{B2} vs. $B_1 = -4.67$, $P < 0.001$; Z_{B3} vs. $B_2 = -2.137$, $P = 0.037$; Z_{B4} vs. $B_3 = -2.818$, $P = 0.005$; Z_{B5} vs. $B_4 = -0.868$, $P = 0.358$). The uterine volume was positively relate to the estrogen dose in B3 and B4 stage ($r = 0.447$ and 0.586 , $P = 0.001$ and <0.0001 respectively), and we found the value of 22ug/kg.d for B3 (value of dose: 17.5, 20, 22, and 23ug/kg.d, $Z = -3.292$, -3.207 , -1.668 , and -1.286 , $P = 0.001$, 0.002 , 0.095 , and 0.119 respectively) and 42ug/kg.d for B4 (value of dose: 35, 40, 42, 45ug/kg.d, $Z = -3.073$, -2.604 , -1.773 and -1.603 , $P = 0.002$, 0.008 , 0.076 and 0.116 repectively) were the most proper as regard to development of uterine volume.

Conclusion: Karyotype and estrogen dose in HRT affected the uterine response to HRT in girls with TS. The uterine development was positively correlated with estrogen dose in stage B3 and B4 and the value of 22ug/kg.d for B3 and 42ug/kg.d for B4 would be optimal in girls with TS who underwent HRT.

P3-223**Indentification of a de novo mutation in the SRY gene in a 46,XY complete gonadal dysgenesis patient with gonadal neoplasia and review of tumor risk in 46,XY DSD patients**

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Objective: To determine the mutation in the SRY gene in a 46,XY complete gonadal dysgenesis patient with bilateral gonadoblastoma and coexisting dysgerminoma. Evaluate the functional consequence of mutated SRY gene in the tumor risk of 46,XY DSD.

Methods and Materials: The proband was a 13-year-old girl who was admitted for examination due to undeveloped secondary sexual characteristics. She had no breast development, menarche, pubic hairs and axillary hairs. Blood samples from the family members were obtained for genetic testing and karyotyping. We summarized 99 patients with a diagnosis of 46,XY DSD from November 1990 to April 2018 to assess the histopathological type and tumor risk of 46,XY DSD patients with SRY gene mutations.

Results: A de novo mutation (c.36dupC/p.13AsnfsGln) in SRY gene in this patient was identified. Through analyzing the recordings of 99 investigated 46,XY DSD patients with SRY gene mutations, a total of 25 46,XY DSD patients (including the patient reported here) with gonadal tumor and SRY gene mutations were identified. And 21 cases were diagnosed as 46,XY complete gonadal dysgenesis (CGD, or Sywter Syndrome) retrospectively, 3 cases had gonadal dysgenesis, and one had gonadal dysgenesis with testicular gonadal syndrome (TDS). The gonadal neoplasia in our patients included gonadoblastoma, dysgerminoma, yolk-sac tumor. We summarized all patients who had undergone bilateral gonadectomy as reported. The total incidence of tumor was 25.25% (25/99) and the malignant rate was 12.12% (12/99). In 25 cases with gonadal tumor, gonadoblastoma (20 cases) and dysgerminoma (12 cases) were considered the most prevalent. And 46,XY complete gonadal dysgenesis patients carried a comparatively highest gonadal tumor risk(12.12%, 12/99), and most of them represented with dysgerminoma in those 46,XY CGD patients, while only one patient had yolk-sac tumor.

Conclusions: In summary, a de novo mutation in SRY gene (c.36dupC/p.13AsnfsGln) in a 46,XY complete gonadal dysgenesis female patient with bilateral gonadoblastoma and coexisting dysgerminoma was identified. Our results futher indicate that mutations in SRY gene can cause abnormal SRY proteins and increase the risk of gonadal tumors.

P3-224

Clinical and laboratory characteristics of different various types of gonadal dysgenesis in girls with hypergonadotropic hypogonadism

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Objective: to evaluate clinical and laboratory characteristics of various types of gonadal dysgenesis in girls with hypergonadotropic hypogonadism.

Methods: 17 girls with hypergonadotropic hypogonadism (13.9 ± 3.72) were examined. Inclusion criteria: characteristics of delayed puberty, no disorders of sex development, presence of müllerian duct derivatives, high levels of gonadotrophins. Tanner stage, antropometric data, bone ages, genitometric parametres, LH, FSH, estradiol, testosterone levels, cytogenetic and molecular genetic tests were provided. Results were evaluated according to the reference rages in girls.

Results: The patients were divided into 3 groups: 46,XY (29.5%, 5/17), 46,XX (23.5%, 4/17) and 45,X (47%, 8/17). Girls with Y chromosome had upper normal height (Me SDS 1.66), 46,XX had average height (Me SDS -0.02, p=0.027) and girls 45,X had low height (Me SDS -3.46, p=0.003, growth failure rate was 87.5% (in 7/8 girls, p = 0.01). There was no difference between bone ages in girls 46,XY (Me SDS -1.6) and 46,XX (Me SDS -1.9, p=0.325), which were low normal while there was delayed bone ages in girls 45,X (Me SDS -3.74, p=0.027). Girls 46,XY had more progressed Tanner stage, then 45,XX, 45,X (Me B3 vs B1 p<0,007, p<0,004). There were no differences between groups in uterus volumes (Me

4.24 vs 1.8 vs 2.1 ml, p>0,05) and in gonadotrophins levels (Me LH 25.1 vs 12.57 vs 25.3 uUI/ml, p>0,05; Me FSH 56.01 vs 88,4 vs 108.7 uUI/ml, p>0,05). Serum estradiol levels in girls 46,XY were higher (Me 44.81 pmol/l) compared with girls 46,XX (Me 13.75 pmol/l, p=0.013) and with girls 45,X (Me 11.29 pmol/l, p=0.028), while there was no difference between two last groups (p=0.82). Serum testosterone levels in girls 46,XY were elevated (Me T 4.6 nmol/l) compared with the levels of same-aged and were higher compared with girls 46,XX (Me T 0.25 nmol/l, p=0.015). Among girls 46,XY 4 out of 5 had bilateral gonadectomies: 2 girls had gonadoblastomas, 1 girl had gonadoblastoma/dysgerminoma and 1 benign Sertoli-Leydig cell tumour. Molecular genetic testings were provided in 46,XY. Heterozygote mutation of gene WT1 was diagnosed in 1 girl.

Conclusion: The following types of gonadal dysgenesis in girls with hypergonadotropic hypogonadism were diagnosed: Turner syndrome, pure gonadal dysgenesis (46 XY, 46 XX). Among 3 groups there were significant differences in girls with Y chromosome: upper normal values of height, more progressed stage of puberty and elevated estrogen and testosterone concentrations. These features can be caused by germ cell tumor.

P3-225

Evaluation of the Role of Fetuin A in Pathophysiology of Polycystic Ovarian Syndrome in Adolescents

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Introduction: Polycystic ovarian syndrome (PCOS); is an endocrinopathy characterised by overlap of hyperandrogenism and hyperinsulinism and chronic anovulation. Etiopathogenesis is still not clearly defined. Fetuin-A is a serum glycoprotein. It is shown to play regulatory functions in many inflammatory processes. We aim to define the relationship of fetuin-A levels with hyperandrogenism and hyperinsulinism in PCOS patients and study the role in pathophysiology.

Method: Adolescent patients with similar age and BMI and diagnosed as PCOS according to 'Endocrine Society Clinical Practice' guides, were included in the study. Subgroups of PCOS and control group were defined as obese and non-obese according to the BMI being above or below BMI $25\text{kg}/\text{m}^2$. Gonadotropin and androgen levels SHBG, results were recorded in PCOS patients. Fasting glucose, insulin, lipid profile, transaminase were recorded in all patients. Cut off value for HOMA-IR was $\geq 3,82$. All patients had blood drawing for fetuin-A and hsCRP. Ovarian size was measured by ultrasonography.

Results: Mean age was $16,4 \pm 1,1$ years in 38 patients with PCOS and $16,2 \pm 0,98$ years in control group(n=40), mean BMI were similar between two groups. Mean Fetuin-A level in PCOS group was significantly higher than the control group (p:0,005). (PCOS: $583,1 \pm 197,45$, control: $460,08 \pm 164,9\text{ng}/\text{ml}$).

Obese-PCOS and Non-Obese PCOS groups were compared:

Fetuin-A, all androgen and SA_I levels were similar. Obese-PCOS patients had significantly lower SHBG and HDL levels ($p=0,012/p:0,017$) and higher cholesterol, LDL, triglycerid, HOMA-IR and HSCRP levels when compared to non-obese PCOS patients ($p=0,014-0,031-0,006-0,015-0,024$).

Obese PCOS and Obese control groups:

In obese-PCOS group, Fetuin-A levels were significantly higher than obese-control group ($p:0,016$). Metabolic parameters and HSCRP levels and all other parameters were similar.

Non-obese PCOS and Non-obese control groups:

Fetuin-A were nearly significantly higher in Non-obese PCOS patients (0,054). All parameters were similar.

Obese-PCOS and Non-obese healthy control groups:

BMI, BMI-SDS, HSCRP and Fetuin-A were significantly higher in obese PCOS patients (0,001-0,001-0,035, 0,013).

Highest fetuin-A level was detected in obese-PCOS group. This was significantly different from obese-control and non-obese control groups ($p:0,016, 0,013$). Also in PCOS group fetuin-A levels was positively correlated with, triglycerid ($r:0,470, p:0,003$), LH ($r:0,416, p:0,009$), LH/FSH ratio ($r:0,381, p:0,018$), total testosterone ($r:0,313, p:0,056$), 1,4 Δ AS ($r:0,441, p:0,008$) and SA_I ($r:0,425, p:0,05$).

Conclusion: Fetuin A levels in our PCOS patients were significantly higher than the control group. In obese PCOS patients, fetuin-A levels were slightly higher than the non-obese PCOS patients and significantly higher than patients in obese control group with similar BMI, lipid profile and HOMA-IR levels. These results put forward the relationship of androgens with Fetuin-A and can direct further studies.

cesarean section 38 weeks of gestation with 3100g from a 39 year-old mother with type 2 diabetes mellitus. There was no disorder in the course of pregnancy. Parents were not consanguineous and her two siblings were exitus by 3 and 4 months of age. On physical examination, her weight was 3.3 kg (50p), height: 52 cm (75-90p), and head circumference was 34 cm (25-50p). Her genital examination revealed normal vagina and no cliteromegaly (Singer stage 5)(Figure 1). The mass 1 ml (gonad?) in the bilateral inguinal region was palpated. An endocrinology study revealed 17 OH progesteron level 31 ng/dL (N,7-77), dihidrotestosteron 114,6 pg/mL (N,5-60), androstenedion 143,8 ng/dL (N,20-290), total testosterone 94,2 ng/dl (N,75-400), LH 11,3 IU/mL, FSH 2,2 IU/mL, low testosterone/androstenedion ratio :0,65 (N>0,8). The karyotype revealed 46,XY. Pelvic ultrasonography showed the presence of testicles in inguinal canal and no ovaries or uterus was observed. 17 β HSD3 deficiency was considered with clinical, radiological and laboratory findings. The genetic study confirmed the mutation p.R80Q (c.239G>A) on gene *HSD17B3* in homozygosity. Multidisciplinary discussed and decided to raise the male sex and was treated with testosterone (IM) at 25mg/month for 4 months in order to increase size of phallus. In the sixth month of treatment, phallus size reached 3.5x1.5 cm (Figure 2). Patient underwent orchiopexy four times in 3, 5, 30 and 33 months of ages; had surgeries of vaginectomy, and correction of hypospadias and chordee at 26 months of age. Figure 3 and 4 show external genital images of the patient between 1.6 and 2.5 years of age.

Conclusion: 17 β HSD3 deficiency cases are diagnosed late in the adolescent period due to virilization or delayed secondary sex characteristics. In early diagnosis, the decision to raise male gender in this cases is important for parents and patients in order to prevent future gender confusion.

P3-226

Rare Cause of 46,XY Sexual Development Disorder: 17 β -Hydroxysteroid Dehydrogenase Type 3 Deficiency

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Introduction: 17 β -hydroxysteroid dehydrogenase type 3 (17 β HSD3) enzyme deficiency is a rare cause of 46 XY disorder of sexual development. It is inherited autosomal recessively and clinical phenotype is highly heterogeneous and depends on the mutation severity. Conversion of androstenedione to testosterone deteriorates due to lack of enzyme.

Objective: In this case report, we present a case who was born entirely in the female phenotype and was grew up as a male sex after the diagnosis of 17 β HSD3 deficiency.

Case: A 3 day old female patient was referred to us because of bilateral mass in the inguinal region. The patient was born by

P3-227

Persistent elevation of gonadotropins in a girl with aromatase deficiency despite adequate estradiol supplementation- A case for reset hypothalamic-gonadal axis

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Background: Aromatase deficiency has been associated with disordered sexual development in infancy and delayed puberty later. The condition responds to estradiol treatment with normalization of gonadotropin levels and pubertal development. We report a girl with a novel Aromatase mutation with persistently elevated gonadotropin levels despite adequate estrogen treatment.

Case Report: This thirteen and a half year old girl was referred for evaluation of delayed puberty and hypergonadotropic hypogonadism. She had presented to an endocrinologist in the neonatal period with clitoromegaly and labioscrotal fusion and was diagnosed as 21 hydroxylase deficiency due to mildly elevated 17OHP levels. Hydrocortisone treatment was associated with lowering of 17OHP level and discontinuation of the drug. Genetic study excluded the diagnosis of 21 hydroxylase deficiency with normal

17OHP levels despite stopping hydrocortisone. She was referred to our clinic with delayed puberty and growth failure (weight 34.8 kg, -1.98 SDS; height of 149.5 cm -1.48 SDS). Investigations showed high FSH (98 mIU/L) and LH (49 mIU/L) and delayed bone age of 10.98 years. Further assessment confirmed maternal virilization during pregnancy suggesting the possibility of aromatase deficiency. Genetic study identified two novel heterozygous mutations on exon 4 (p.Arg115Ter) and exon 5 (p.Tyr184Ter) of aromatase gene. Pubertal induction was initiated with low dose estradiol valerate (0.25 mg daily) and gradually increased to 1 mg over 2 years. This was associated with increase in body mass index from 15.6 kg/m² (-1.65 SDS) to 19.7 kg/m² (-0.14 SDS), breast size from stage II to stage V and bone age from 10.98 years (at chronological age of 13.5 years) to 13 years (at chronological age of 15.5 years). Estradiol replacement was however not associated with reduction in gonadotropin levels (LH 36.97 mIU/L and FSH 106.9 mIU/L) or increase in uterine size and endometrial thickness. This is in contradistinction to previous reports where estradiol treatment resulted in normalization of FSH levels and may be related to reset hypothalamic-pituitary-gonadal axis due to severity of aromatase deficiency in our girl.

Conclusion: Persistent gonadotropin elevation in our case despite adequate estradiol replacement indicates abnormal pituitary responsiveness to estradiol and needs to be further explored.

P3-228

Comparison of Classical and Non-Classical Turner Syndrome at NICH Karachi

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Objective: To analyse chromosomal abnormalities of the patients who were referred for the screening of short stature and delayed puberty and to verify the association between karyotype and phenotype in confirmed Turner Syndrome (TS) patients.

Study Design: Descriptive study.

Place and Duration of Study: Department of Pediatric Endocrinology and Diabetes Unit-II, National Institute of Child Health, Karachi, from January 2011 to June 2016.

Methodology: Patients referred for the evaluation of short stature or delayed puberty were for the assessment of karyotype and phenotype correlations; standard karyotyping was executed and analysed on the basis of routine G-banding technique. Echocardiography and pelvic ultrasonography was also performed.

Results: The study population consisted of 79 registered patients, with short stature and delayed puberty 48/79 (60.75%), short stature 68/79 (86.07%), and ambiguous genitalia 5/79 (6.32%). Conferring to the karyotype analysis, classical Turner Syndrome 45, X was found in 42/79 (53.16%), isochromosomes 13/79 (16.45%), and mosaicism was present in 11/79 (14.1%). Only 7/79 (8.86%) cases were diagnosed in infancy.

Conclusion: The results of the study showed the consistency of short stature and delayed puberty in most of patients. Monosomy of X chromosome was the commonest followed by isochromosomes, mosaicism and structural abnormalities of X chromosome. No remarkable difference was found among classical and non-classical TS patients' height.

P3-229

Primary amenorrhea revealing Leydig cell hypoplasia

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Introduction: Leydig cell hypoplasia (LCH) or agenesis, is an autosomal recessive condition and a well-defined form of 46,XY disorder of sex development (DSD) resulting from inadequate foetal testicular Leydig cell differentiation.

Inactivating mutations in the luteinizing hormone/chorionic gonadotropin receptor (LHCGR) gene account for the underlying LCH pathogenicity

Case Report: We studied a 15-year-old female who presented at the Department of Endocrinology for primary amenorrhea. The patient was born at full term after an uncomplicated gestation of healthy consanguineous parents. A similar history with a female cousin was reported. Physical examination showed infantile breast development and absence of pubic hair growth. She had female external genitalia appearance with the external opening of urethra and short hypoplastic-two-centimetre-length vagina under a hypertrophic clitoris. Hormonal assessment showed plasma testosterone level at 0.38 ng/ml, which did not change after administration of human chorionic gonadotropin.

Luteinizing hormone (LH) plasma level was elevated at 60mUI/ml and was hyper-responsive after stimulation test with Luteinizing hormone-releasing hormone (LHRH). Estradiol was significantly low (<9 pg/ml) and serum FSH level was 6,4 mU/ml in the reference range.

Pelvic ultrasound showed two testes in inguinal regions, but no Müllerian structures.

Genetic analysis revealed that the karyotype was 46,XY and a homozygote nonsense mutation of LHCGR was confirmed. The same mutation was found heterozygous after genetic analysis of the parents DNA.

Our patient underwent a bilateral gonadectomy and a hormonal replacement with oestrogen was started. At histology analysis no Leydig cells were seen.

Conclusion: We conclude that this case of female DSD was due to a Leydig-cell agenesis. 46,XY patients who are usually raised as female social gender may manifest ambiguous genitalia with elevated LH and decreased testosterone. Hormone tests are powerful tools and gene testing is helpful to establish the diagnosis.

P3-230

Novel heterozygous mutation in Wilms tumor 1 gene in patient with mixed gonadal dysgenesis

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Disorders of sex development (DSD) have been defined as congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical. Wilms tumor 1(WT1) gene mutations have been described in 46,XY patients with ambiguous genitalia or complete gonadal dysgenesis with or without Wilms tumor, nephropathy, gonadoblastoma and other defects e.g. cryptorchidism, hypospadias. Sex chromosome mosaicism is a major cause of DSD with a wide phenotypic variability. The phenotype is primarily dependent on the proportion of each cell line in the developing gonads. This study reports one year old infant, reared as a male, presented with ambiguous genitalia. According to clinical investigations of the gonadal phenotype, gonadal histopathology and the karyotype, our patient was clinically diagnosed to have mixed gonadal dysgenesis (MGD). Furthermore, pelvic ultrasonography showed moderate pelvicalyceal dilatation in the left kidney. Cytogenetics studies have detected two cell lines by karyotype analysis of blood lymphocytes 45,X[90]/46,X,idic(Y)(q11.2)[10]. FISH was also applied on gonadal cells and showed the same type of sex chromosome mosaicism, but with different distribution. Sequencing analysis of WT1 gene showed that the patient has a novel heterozygous missense mutation in exon 9. In silico functional studies predicted the pathogenicity of the mutation. This is the first study to report a mutation in WT1 in MGD patient. This study demonstrates the importance of WT1 in male sexual differentiation and kidney development.

P3-231

Falsely elevated serum sex steroid hormones in a girl with premature adrenarche

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Background: Laboratory evaluation is crucial for accurate assessment of patients with endocrine disorders. When clinical picture is in obvious contradiction with laboratory results, one should suspect and prove analytical interference.

Case Presentation: a 6.7-year-old girl presented with sexual and axillary hair accompanied by adult-type body odor. She was tall (height SDS 2.6), with no other signs of virilisation and no

breast development. Her bone age was slightly advanced (7.5 years), and laboratory workup showed markedly elevated levels of dehydroepiandrosterone sulphate (DHEAS), elevated testosterone and appropriate level of 17-hydroxyprogesterone (17-OHP) measured by electrochemical luminescence immunoassay (ECLIA). Subsequent investigations confirmed previous laboratory results, but also revealed elevated serum estradiol with no evidence of estrogen effect on uterus and no adrenal or adnexal mass. Cortisol level was unremarkable. During one year follow up, there were no changes in girl's clinical appearance, while levels of her sex steroids determined by ECLIA fluctuated from undetectable or slightly elevated to markedly elevated. There were no apparent risk factors for analytic interference (no biotin supplementation or drugs, negative rheumatoid factor, no hypergammaglobulinemia). When samples were reanalyzed with the addition of a blocking agent, significantly lower levels of serum sex steroids were obtained, while liquid chromatography-tandem mass spectrometry (LC-MS/MS) revealed sex steroids appropriate for age.

Conclusion: Laboratory interference is a drawback in hormonal testing. Clinicians should have that in mind when faced with laboratory results discordant with patient's clinical presentation. Elevation of multiple sex steroid hormones in a prepubertal girl due to laboratory interference in immunoassay was finally unmasked by LC-MS/MS.

P3-232

NR5A1 Gene Mutation: Variable Phenotypes, New Variants, Different Outcomes

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Introduction: NR5A1 (nuclear receptor subfamily 5 group A member 1) is a transcriptional regulator of adrenal and gonadal development and function. Heterozygous and homozygous NR5A1 mutations have been described in 46,XY disorders of sex development (DSD). The clinical, endocrine and genetic features of three 46,XY children from two unrelated families (A and B) with NR5A1 genetic variants are reported.

Patients and Methods: Two sisters from family A and a boy from family B were studied. Endocrine parameters were assessed by standard laboratory methods. NGS analysis was performed using Sure Select (Agilent) customized DSD panel and captured products were sequenced by MiSeq (Illumina)

Results: Two sisters (14.5 years; 13.9 years) were referred for evaluation of absent pubertal development. On clinical examination, they showed breast development Tanner Stage 1, pubic hair Tanner Stage V. Genital examination demonstrated clitoromegaly,

and presence of a single orifice compatible with persistence of the urogenital sinus. Endocrine assessment demonstrated low estradiol levels with elevated gonadotrophins in both the sisters (basal FSH 87.49 IU/L and 135.10 UI/L respectively, basal LH 20 IU/L and 30 IU/L, respectively). Increased testosterone for females normative values were also found. Karyotype was 46, XY. Pelvic ultrasound did not show any Müllerian structures; gonads were not individuated. According to parents, female sex was confirmed in both sisters after deep psychological investigation and gonads removed. The boy presented at the age 18 months for bilateral undescended testes and severe peno-scrotal hypospadias. At puberty, he showed slow pubertal progression with low testicular volume. His endocrine data demonstrated hypergonadotropic hypogonadism (FSH 63 IU/L; LH 14.4 IU/L; testosterone 2.5 ng/ml) and normal adrenal function. Using a DSD 14-gene next generation sequencing (NGS) panel, we identified two heterozygous missense NR5A1 variants in the patients: c.248T>A, p.Val83Glu in the sister; c.937C>T, p.Arg313Cys in the boy. The former was predicted pathogenetic by *in silico* analysis, the latter was reported in HGMD database (CM118686) and previously identified in 46,XY DSD Italian patient. Sex related hormonal substitutive therapy was started. All the children presented good psycho-social outcome according to assigned sex.

Conclusions: Present data confirmed that NR5A1 gene mutations may present with variable genital phenotypes. Anyway, reproductive function was impaired. Any clinical or endocrine data seem to be unable to differentiate these patients from other 46,XY DSD. In persons with NR5A1 mutations, different decisions in sex assignment may permit good somatic and psychological outcome, but any option requires optimal substitutive therapy.

P3-233

Early embryonic testicular regression syndrome presenting with female external genitalia

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Introduction: Testicular regression syndrome (TRS) is a rare disease characterized by testicular dysfunction that causes varying degrees of virilization defect according to the emergence period in fetal life. The majority of cases present with normal male external genitalia. However, ambiguous genitalia or, more rarely, female external genitalia can be found depending on the extent and timing of the intrauterine accident. Here, we present a case of TRS with normal female external genitalia, mullerian remnants and streak gonad.

Case: Fifteen-year old female patient was admitted to our outpatient clinic due to primary amenorrhea and absence of breast development. She was born after uneventful pregnancy with birth-weight of 2250 gram at 38 gestational weeks. There was no remarkable family history and she has two healthy brothers. The parents were relatives (first-degree cousin). On physical examination, weight was 53.3 kg (-0.28 SDS), height 160.9 cm (-0.12 SDS), blood pressure 100/60 mmHg, and the rest of systemic examination was unremarkable. According to Tanner stage, pubic hair was stage 3-4 and breast development was stage 1. She has normal female external genitalia with separate vaginal and urethral openings and there was no clitoromegaly or palpable gonad. Laboratory examination revealed normal kidney-liver-thyroid function tests, ions, morning cortisol / ACTH, and DHEA-S. In addition, LH (39.4 mIU / mL) and FSH (83.0 mIU / mL) were markedly high; estrogen, anti-mullerian hormone, and inhibin B levels were low. Pelvic ultrasonography and MRI showed no uterus or gonads. The lumbar region bone mineral density was decreased (L1-4 0.554 g / cm²; -4.46 SDS). Karyotype was 46, XY and SRY was positive. Further genetic analysis by next generation sequencing of genes involved in the development of gonad revealed no mutation. Laparoscopic evaluation showed mullerian structures (rudimentary uterus and fallopian tubes) and streak gonads. Bilateral gonadectomy was performed. The pathological examination revealed spermatic cord, immature seminiferous tubules, and Leydig cell groups in the stroma. There was no evidence of neoplasia. Estradiol treatment for pubertal progression was started.

In Conclusion: Antenatal or perinatal vascular thrombosis or torsion are thought to be the causes of TRS; however, the precise etiology has yet been identified. Patients with TRS present with different phenotype depending on the occurrence period of testicular dysfunction. However, female external genitalia are rarely reported. TRS should be kept in mind in cases with female external genitalia but male karyotype with 46,XY, elevated gonadotropins, and mullerian remnants.

P3-234

Diagnostic Dilemma in a 46 XY Female

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Introduction: Disorders of sex development (DSD) are conditions with discrepancies between the chromosomal, gonadal, and phenotypic sex. We present a case of a phenotypic 46 XY female with primary amenorrhea and full thelarche, presence of Mullerian structures, elevated testosterone with no virilization, and bilateral adnexal masses. Our differential diagnosis included Androgen Insensitivity and Gonadal Dysgenesis.

Case Description: A previously healthy phenotypic female presented with primary amenorrhea at 17-years-of-age. She had thelarche onset at age 10 and she progressed to Tanner Stage V breast development. She had no virilization or symptoms to suggest adrenal insufficiency. She endorsed pelvic fullness. Family history was negative for amenorrhea or fertility concerns.

Physical examination revealed a tall (height 187.3cm, 100th percentile) and lean body habitus. She has broad hands and long fingers. Pubertal assessment showed Tanner Stage V breast development and Tanner Stage V pubic hair. Prader score was 0. An examination under anesthesia demonstrated a normal appearance of the vagina, cervix, uterus and fallopian tubes.

Laboratory investigations included an elevated beta-HCG (93 IU/L, reference range <5 IU/L), elevated FSH (43 U/L), and elevated testosterone (3.8 nmol/L, reference range 0.5-2.0nmol/L). A pelvic MRI showed large bilateral adnexal masses with the left and right diameter measuring 9.4 cm and 8.3 cm respectively. Genetic testing identified a *heterozygous* pathogenic variant in POR gene responsible for P450 oxidoreductase deficiency (PORD), a rare form of congenital adrenal hyperplasia.

Pathology of the adnexal masses identified bilateral dysgerminomas arising in gonadoblastomas, with no discernible underlying gonadal tissue. There were no metastases.

Discussion: Despite progressive understanding of DSD and the increasing role of genetic testing, challenges in diagnosis persist. We suspect partial gonadal dysgenesis in this case given the presence of Mullerian structures and malignant gonads. We hypothesize that there was adequate function of dysgenetic gonads for full thelarche, before malignant transformation. The dysgerminomas then produced testosterone, accounting for elevated levels but minimal virilization. The identified heterozygous mutation for PORD is insufficient to explain her phenotype, however; we question if she has a secondary, unidentified compounding mutation. She has no clinical or biochemical features to suggest PORD.

This case highlights the challenges in diagnosing patients with 46 XY DSD, where 80% of causes of gonadal dysgenesis are unknown, and reinforces the value of a multi-disciplinary approach including genetic and endocrine expertise in diagnostic evaluation.

P3-235

Leydig Cell Hypoplasia in Three Siblings in the Same Family

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Background: Leydig cell hypoplasia (LCH) is a rare disease and one of the causes of male disorder of sexual differentiation (DSD). Inactivating mutations in the luteinizing hormone/chorionic gonadotropin receptor (LHCGR) gene can produce LCH. In this poster, we present three siblings with LCH based on the clinical and laboratory findings and the molecular diagnosis.

Cases: A seven-year-old child was brought to our hospital for inguinal gonads. Physical examination was characterized by a predominantly female phenotype, a blind-ending vagina, and no Mullerian structures. Chromosomal analysis revealed 46 XX karyotype. SRY gene was normal. The sequence analysis of the LHCGR gene showed a homozygous mutation (p.A483D

c.1448C>A). When other siblings were examined, they were found to have the similar physical findings and the same genetic abnormality.

Conclusion: We identified a homozygous mutation in the LHCGR gene. The variable phenotype in LCH suggested variable expressivity of the disease.

P3-236

Klinefelter Syndrome Presenting with Learning Disabilities: Case Reports

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Introduction: Klinefelter syndrome (KS) occurs in approximately 1 in 650 males, representing the most common sex chromosome disorder. However, it is estimated that only 25% of KS patients are ever diagnosed, and 90% of them are not identified until 15 years of age. The disease is caused by congenital aneuploidy of the sex chromosomes; the most usual karyotype being 47, XXY. Typical phenotype includes tall stature, hypergonadotropic hypogonadism, small testicular volume, and fertility issues. Characteristic neurocognitive, behavioral, and language deficits of varying severity have been reported in patients with KS, including verbal disabilities, learning disabilities, executive function impairments, psychiatric disorders, autism spectrum disorders, and attention-deficit / hyperactivity disorders.

Case Reports: An 11-year-old boy was referred to the Pediatric Endocrinology Outpatients Unit of our Hospital due to obesity. The parents reported nothing unusual in their son's medical history, except from learning disabilities and behavioral issues. The boy primarily exhibited social and emotional developmental delays, as well as school difficulties, including deficits in speech and language skills. The child's height was 155 cm (95th percentile) and he weighed 60 kg (>95th percentile), with a BMI of 24.97 (>95th percentile). On physical examination, sexual maturity rating of his gonads, pubic hair and axillary hair were at stage 1. Additionally, gynecomastia was noted. Laboratory testing revealed prepubertal FSH, LH and testosterone levels. Chromosome analysis detected a 47,XXY karyotype. We also report the case of another 11-year-old boy with KS who initially presented 5 years ago with prominent learning disabilities and speech difficulties. Developmental milestones were slightly delayed. Physical examination and past medical history were unremarkable. Cytogenetic analysis eventually revealed the diagnosis. The child has been receiving speech, occupational and behavioral therapies for the last 5 years. These interventions have greatly improved behavioral and learning skills.

Conclusion: Although many individuals with KS become highly successful in their academic pursuits and social lives, it is clear that there is a distinct behavioral and neurocognitive phenotype associated with the extra X chromosome. As the learning disabilities, speech delays, and behavioral difficulties usually develop in childhood they present a unique opportunity for early detection of KS and timely intervention. Clinicians should therefore maintain a high level of vigilance for KS in boys with learning difficulties.

P3-237

Gender self-identification and intra-family relations in children with disorders of sex development

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Introduction: The birth of a child with disorders of sex development (DSD) requires a long-term strategy of monitoring and treatment which is carried out by a multidisciplinary group of professional physicians, with a mandatory understanding of the psychosocial problems in a child and parents.

Materials and Methods: Gender self-identification was investigated in 20 children and adolescents with DSD aged 1.5-17 years. To determine gender identity, we used the methodology of "Homunculus", to assess gender socialization - the Wartegg method of spontaneous drawing, to assess internal family relations - the method "My family" and the method of structured interviews. An assessment of intra-family relations was done also in a control group, which included 28 families with healthy children. All DSD patients carried out a cytogenetic test, and, if necessary, fluorescence in situ hybridization (FISH).

Results: In DSD group, chromosomal DSD was diagnosed in 6 (30%), 46,XY DSD - in 13 (65%) and 46,XX DSD - in 1 (5%) patients. Diagnosis of DSD was established in different age: from birth to 16 years old, on average at 7,26 [1,50; 13,00] years. Disorders of gender identity in children with DSD did not depend on the child's age, the karyotype, or gender of the child's civil registration ($p>0.05$). 54.25% of families with DSD child did not seek to have children in the future because of the fear of having a child with genetic disorders again. The frequency of divorces in the families with DSD children did not depend on the presence of a DSD child and his age ($p>0.05$). In 25.0% of families, children had often been criticized, and negatively assessed by parents, which worsened the formation of a child's gender identity. The issue of gender self-identification and intra-family relationships in children with DSD is an important issue that requires further study and analysis of data obtained from a larger cohort of patients.

Conclusions: The psychological support of children with DSD and their families is an important component of comprehensive medical and social rehabilitation.

P3-238

Bilateral testicular atrophy and normal Inhibin B level: A paradoxical clinical finding for a rare biochemical cause!

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Background: Testicular atrophy is a rare complication following inguinal hernia repair particularly in children<2 years and those with an undescended testis at highest risk> with an undescended testis. Inhibin B is secreted from the testis as a product of Sertoli cells, and has been suggested as a good marker for spermatogenesis. Its value is expected to be very low in children with bilateral testicular atrophy

Case Report: A 7-year-old child underwent surgery at 6 years for undescended testis. Intraoperative exploration shows two very small testis : the right one was fixed in the scrotum, the left one was left was fixed in the pubis. On examination, we found a normal penis of 6 cm and 2 non palpable testes. Karyotype : 46,XY. Hormonal balance shows : normal FSH and LH levels, low levels of testosterone < 0,025 ng/mL before and after HCG test, AMH < 0,01 ng/mL and surprisingly a normal level of inhibine B : 113 ng/mL controlled at 139 ng/mL. We seek first for an extragonadal production of Inhibine B but AFP and B HCG were normal. We though seek for the ELISA assay technique (of Beckman Coulter) and blood samples were addressed for a dosage using the less common ELISA technique of Anshlabs. Inhibine B was then found to be undetectable (<4,6 pg/mL). Fertility is thus found to be compromised. The child will receive a testosterone replacement therapy when aged 12 in addition to bilateral testicular prosthesis.

Discussion: Heterophilic antibodies are present in a significant proportion of the population, and are likely to give a false-increased result in sandwich assays (such as the inhibin assay). They are thought to be produced following immunization with animal proteins (mouse, rabbit, goat, sheep etc.). In particular, a vaccine produced on rabbit cells had been the cause of false TSH results in the 1980s. This interference can be found nowadays in 1 serum/10 000.

Conclusion: Hormonal assays are often the diagnostic pivot in pediatric endocrinology. Being aware of biochemical causes of paradoxical hormonal dosages can be a key to avoid unnecessary additional explorations.

P3-239

Normosmic Hypogonadotropic Hypogonadism: An Intrafamilial Case

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Background: Idiopathic hypogonadotropic hypogonadism (IHH) is due to the failure of gonadotropin releasing hormone (GnRH) secretion which impairs the physiological initiation of puberty. About 30 to 50% of IHH is associated to hereditary causes and about 50 mutated genes have been identified.

Objective and Methods: We present three intra-familial cases of normosmic IHH (nIHH) related to a new association of two heterozygotic TACR3 mutations.

Case Report: The index case reports to a 16 year-old male with no pubertal development at this age. Later on, two of his three sisters also presented complete hypogonadism. All cases had a normal sense of smell. Investigation showed low sex steroid and gonadotropin levels and no evidence of a mass lesion in the cerebral MRI. The diagnosis of nIHH was supported by the identification of two heterozygous mutations on TACR3 gene: c.824G>A (p.Trp275*) and c. 689G>A (p.Arg230His) in all subjects. Although the former mutation was previously described as pathogenic by the literature, the latter was classified as of uncertain significance at date. The present family cluster supports the evidence of the pathogenicity of the second variant.

Conclusion: Congenital IHH is a very rare genetic disorder that if undiagnosed or untreated may lead to infertility associated to complete or partial absence of GnRH. TAC3/TACR3 mutations have a critical importance on sexual maturation and are an important genetic cause of nIHH that should be particularly searched in patients with high serum FSH/LH ratio. The treatment of nIHH is based on sex steroids replacement, therefore promoting the pubertal development.

P3-240

Testicular regression syndrome A Clinical and Pathologic Study of 4 Cases

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Introduction: Testicular regression syndrome (TRS) also called vanishing testes syndrome is a rare developmental disorder that represents less than 5% of cryptorchidism cases. It is characterized by the absence of one or both testicles with partial or complete absence of testicular tissue. TRS phenotypes are various depending

on the extent and timing of the intrauterine accident during fetal sexual development.

Material and Methods: Our study will concern 4 cases of TRS treated in Mohamed VI university hospital between 2015 and 2019.

The mean age at diagnosis was 41 months (2 months - 11 years). Clinical examination noted bilateral cryptorchidism in all ours patients, 3 of them presented with micropenis and only one had gynecomastia. All our patients carried a male karyotype (46XY). The average AMH and testostérone values were respectively 2.4 ng/ml and 0.12 ng/ml. Pelvic ultrasound and pelvic MRI findings showed total absence of testicular tissues in three cases, while one of them presented a hypotrophic unilateral testicle. Three patients had an exploratory laparoscopy with a benign pathological study and all of them were treated by androgen replacement therapy and were followed up in our department.

Discussion/ Conclusion: The descent of the testes appears to be under the control of several hormonal and mechanical factors, but no specific factor has yet been identified for the pathogenesis of undescended or non palpable testis. TRS is thought to be the result of late antenatal or perinatal vascular thrombosis or torsion or more unlikely an endocrinopathy.

Theoretically, TRS carries a potential for malignant degeneration in the long term outcome and therefore removal of any remnant tissue is a common practice to eliminate this risk. However, no case series has reported germinal dysplasia or intratubular germ cell neoplasia in any of the specimens taken from these patients and there is still controversy regarding the optimal management of the testicular remnant in cases of TRS. Reason why the management of TRS cases has to be discussed in multidisciplinary conceration meetings.

P3-241

46XY, DSD with hemolytic uremic syndrome as the primary manifestation——Denys-Drash syndrome caused by WT1 gene mutation

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Objective: To summarize the diagnosis and treatment of a rare 46XY DSD cause: Denys-Drash syndrome.

Methods: To summarize the clinical manifestations, laboratory tests, diagnosis and treatment of a rare 46XY DSD cause presenting with hemolytic uremic syndrome: Denys-Drash syndrome (WT1 mutation).

Results: Female, 2 years and 4 months, were admitted to the hospital at 2018-11-7 because of “edema, reduced urine output for 3 weeks”. 2018-10-18 laboratory tests in other hospital: urinary protein 3+, RBC 2+, blood Hb 69g/L, PLT 82x10⁹/L, blood UREA 77.2mmol/L, CREA 961umol/L, combined with hypertension (BP 130/90mmHg). Then CRRT was given to the patient and “sodium nitroprusside” was given to control the blood pressure and other supportive treatment. The child’s edema was reduced and blood

pressure was well controlled. But there was still no urine output. Past history, personal history, and family history are not abnormal.

Physical Examination After Hospitalization: Weight: 12Kg (-1SD) Height: 86cm (-3SD), moderate anemia, mild edema, no abnormal findings in the lungs heart or abdomen. Female vulva, no clitoris hypertrophy. The testicles are not touched on both sides of the labia majora.

Laboratory Examination: blood Hb 66g/L, PLT 494x10⁹/L, reticulocyte ratio 0.0539, reticulocyte absolute value 0.1093x10¹²/L, blood UREA 21.5mmol / L, CREA 392umol / L. Blood smear: RBC size is uneven. Color Doppler: the size of the left kidney was 6.4 x 3.0 cm, and the size of the right kidney was 6.2 x 2.4 cm. Gonadal color ultrasonography: bilateral dysplasia testis can be seen in the abdominal cavity. Chromosome karyotype is 46, XY. Gene testing: the WT1 gene undergoes de novo mutation, which is a heterozygous mutation, a missense mutation, c.754G>A, resulting in amino acid change p. D252N.

Our children are currently treated with symptomatic treatments such as antihypertensive and EPO and peritoneal dialysis. Pre-transplantation gene matching has been completed and a kidney transplant is planned. This child is currently being raised as a girl. Because of the high risk of malignant tumors in the gonads of the child, it is planned to have a gonadal resection during kidney transplantation.

Conclusion: Acute/chronic renal insufficiency in infants and young children may be caused by genetic factors. In addition, patients with gonadal dysplasia should be alert to the possibility of WT1 gene mutation.

Results: The reason for the initial treatment of all patients was ambiguous genitalia.

Age Verification Diagnosis: Up to 1 month y 60% (6/10) of children with mosaicism and in 76% (13/17) of children with partial gonadal dysgenesis ($p=0,31$), up to 1 year — in 10% (1/10) vs 6% (1/17, $p=0,6$) and up to 3 years — y 30% (3/10) vs 18% (3/17, $p=0,38$).

Male gender selected in 76% of patients in group with mosaicism and in 60% - with partial gonadal dysgenesis ($p=0,31$).

Mediana (Me) EMS was 4,5 [1;10] in patients with mosaicism and 1,25 [1;5] – with DSD 46,XY, partial gonadal dysgenesis ($p=0,033$).

Functional state of the pituitary-gonadal system: elevated values FSH were in 60% (3/5) of patients with DSD 46,XY, partial gonadal dysgenesis (64,8; 20,1; 12,8 mIU/ml) and in 10% (1/10) of patients with DSD 45,X/46,XY (11 mIU/ml, $p=0,07$). Elevated values LH were in 60% (3/5) of patients with DSD 46,XY, partial gonadal dysgenesis (26,5; 12,6; 16,68 mIU/ml) vs 11% (1/9) with DSD 45,X/46,XY (19,27 mIU/ml, $p=0,09$).

Functional state of the gonads with mosaicism and partial gonadal dysgenesis: Me AMH 41,15 [1,75;168,6] vs 16,77 [1,97;44,5] ng/ml ($p=0,049$), Me ΔT 9,47 [1,37;29,8] vs 4,93 [0,23;7,96] nmol/l ($p=0,047$), Me inhibine B 165,1 [111,9;341,4] vs 64,8 [2;356,6] pg/ml ($p=0,32$).

Conclusion: So, patients with DSD 45,X/46,XY in comparison with DSD 46,XY partial gonadal dysgenesis had safer gonad function and more pronounced degree of masculinization of the external genitalia, what to consider during rehabilitation of this group.

P3-242

Clinical and Laboratory Characteristics of Patients With Different Variants of Gonadal Dysgenesis

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Objective: To study clinical and laboratory characteristics of patients with disorders of sex development (DSD) 45,X/46,XY and 46,XY, partial gonadal dysgenesis.

Subjects and Methods: It was included 27 patients with disorders of gonadal dysgenesis at birth to 9 years, which were divided into groups based on cytogenetic survey – DSD 46,XY, partial gonadal dysgenesis (n=10) and DSD 45,X/46,XY (n=17).

Gonadal Dysgenesis Criteria: Mosaicism 45,X/46,XY, derivats Mullerian duct with 46,XY.

All children evaluated the structure of the external (External Masculinization Score, EMS, 0-12, n=27) internal genitalia (by pelvic ultrasound, n=27, laparoscopy, n=25), hormonal research in mini-puberty (follicle-stimulating hormone, FSH, n=15, luteinising hormone, LH, n=14, inhibin B, n=9), in mini-puberty and neutral period (anti-Mullerian hormone, AMH, n=24, basal testosterone and after the human chorionic gonadotrophin stimulation test, ΔT, n=22)

P3-243

Etiologic Classification of 46, XY Disorders of Sexual Differentiation According to Chicago Consensus: Single Center Results

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Objective: The aim of the study was to describe the etiologic diagnosis, clinical characteristics in children with 46,XY disorder of sexual development (DSD).

Methods: The 125 46,XY patients were included the retrospective study. The definitive diagnosis was made by presentations and clinical findings, gonadal morphology and genital anatomy of patients, basal and stimulated hormone results, imaging methods and molecular genetic analyzes. All data obtain from hospital records.

Results: Types and ratios of each presentation of the 125 patients with 46,XY DSD were as follows (Table) Disorders of testicular development(8%), disorders of androgen synthesis or action (16%), other causes (57.6 %) and associate with syndromes (%). Among the other causes etiology were as hypospadias (43.2%), undescended testis (16.2%) and micropenis (36.1%). Hypospadias was detected in a patient with CYP21A2 mutation. Sixteen patients were raised as girls. 55 patient' parents were consanguineous. Brothers of thirteen patients and cousins of five patients' also have similar disorders.

Conclusion: The most common etiological diagnosis in 46 XY DSD was hypospadias. Defects in androgen synthesis and action as etiological causes of DSD were at the same frequency with associate with syndromes in this study. Ovotesticular DSD was rare.

	No	Raised gender as
46, XY DSD (n:125)		
A-Disorders of testicular development		
1-Complete gonadal dysgenesis		
9p del	1	F
WT1	1	F
2-Testicular regression syndrome	5	M
3- Ovotesticular DSD	3	1F, 2M
B-Disorders of androgen synthesis or action		
1-Androgen synthesis defects		
a-Smith-Lemli-Opitz syndrome	1	M
b-20,22 Desmolase deficiency	1	F
c-3 BHSD deficiency	2	M
d-17 Hydroxylase deficiency	1	F
e-5α Reductase 2 mutation	4	2F, 2M
f-21 Hydroxylase deficiency and hypospadias	1	M
4-Disorders of androgen action		
a-CAIS	9	9F
b-AMH-R defect	1	M
III-Others		
a-Hypospadias	29	M
b-Hypospadias and Micropenis	2	M
c- Hypospadias and undescended testis	1	M
b-Epispadias	2	M
c-Undescended testis	12	M
d-Micropenis	23	M
e-Micropenis and undescended testis	3	M
IV-Associate with syndromes		
a-Robinow	4	M
b-Simpson Golabi Behmel	1	M
c-Micro	2	M
d-Miller Dieker	1	M
e-Cri du cat	1	M
f-Bardet Biedel	1	M
g-Multiple Pterygium	1	M
h-Noonan	8	M
i-VAGR/VATER/VACTERL	4	M

P3-244

Four-year experience of a new referral center for gender non-conforming children and adolescents in North-East of Italy

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Objectives: To describe the patients with gender non-conforming referred to a pediatric medical center after creation of the multidisciplinary team “APEVAGE” (Ambulatorio Pediatrico per la Varianza di Genere, Pediatric Clinic for Gender Variance) composed by pediatric endocrinologist, psychologist and child psychiatrist at Institute for Maternal and Child Health “Burlo Garofolo” in Trieste. It is one of the 8 centers recognized by ONIG (Osservatorio Nazionale sull’Identità di Genere, National Observatory on Gender Identity) and the only one in the North-East of Italy (1,882,988 inhabitants <18 years of age over a total of 11,640,852 inhabitants).

Methods: Data gathered on 15 consecutive patients <18 years, with initial visits between April 2015 and March 2019, who were referred to APEVAGE for gender nonconformity. Main descriptive measures included gender, age, source of referral, final diagnosis (if available).

Results: Fifteen patients have been evaluated so far. The clinic started in 2015 with the first patient. There was an increase in the following years: in 2016 2 patients, in 2017 4 patients, in 2018 6 patients and 2 patients in the first 3 months of 2019.

Genotypic male:female ratio was 6:9 (2:3). Age of presentation was 10.6 years [10.1-15.5] (median [IQR]) which was higher for female (15.2 [10.4-15.9] vs 10.5 [7.4-10.5], p=0.05). Seven patients (46%) were referred by primary care pediatricians, 4 by psychologist or child psychiatrist (27%), 3 by hospital pediatrician (20%) and 1 by parents self-referral (7%). In 2 patients (median age 14.9 years) a diagnosis of gender dysphoria have been established, but no medical treatments have been started so far (in one case due to disagreement between parents, in one case pending approval); 7 patients were identified as gender variant (median age 8.0 years) and did not require further evaluations; 2 patients had a disorder of sex development (Frasier syndrome and 5-alpha-reductase deficiency); 4 patients are currently under evaluation.

Conclusions: After establishment of a multidisciplinary gender clinic, there was a six-fold increase in referred patients, although the prevalence of children and adolescent referred is still very low (0.79/100.000 minors). Girls are more frequently referred than boys, with a higher age at referral. The majority of patients had been referred by primary care pediatricians. No patients were treated with pubertal suppressive therapy (due to a too advanced pubertal development), nor cross-sex hormone therapy. A greater awareness is needed in this region of Italy.

P3-245

Ovarian insufficiency: The hidden uterus

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Gynecologic anomalies, including uterine agenesis and ovarian dysgenesis, are reported in clinical practice of reproductive endocrinology. They are some of several differential diagnoses in adolescent females with primary amenorrhea and delayed puberty. Primary ovarian insufficiency can be determined by conducting sex hormone tests to evaluate the hypothalamic-pituitary-ovarian axis, but accurate confirmation of Mullerian agenesis can be extremely challenging by image modalities. We report a case of a seventeen years old female, 46 XX karyotype, with ovarian dysgenesis and a presumed diagnosis of uterine agenesis which was proven incorrect after post estrogen replacement. A diagnosis of an absent uterus may bring psychological trauma to patients and families, which will have significant implications on future fertility options. No conclusion should be made regarding the status of the uterus until adequate exposure to exogenous estrogen has been completed and reassessed.

MRI scan confirmed no uterus and ovary identified, bilateral undescended testes in inguinal regions and hypoplastic vagina.

Paediatric urologist and paediatric gynaecologist had been consulted. Examination under anaesthesia revealed right gonad at superficial inguinal pouch and left gonad inside inguinal canal. External genitalia favoured female phenotype with normal-looking labia majora and underdeveloped labia minora, separate urethral and vaginal openings at introitus, phallus enlarged measured 4cm in length and 1.6cm in width. Cystoscopy showed normal-looking female type urethra, normal bladder with bilateral ureteric orifices at orthotopic position. Vaginoscopy showed blind-ended vagina lined by normal-looking mucosa with length of 4cm, no cervical opening seen.

Whole exome sequencing revealed no mutation in SRD5A2 gene but a missense mutation c.2591T>A (p.Leu864Gln) in AR gene. This mutation has been found previously in a case of complete androgen insensitivity syndrome. The underlying pathology had been explained to the parents and the girl. The gender options and subsequent management had been counselled. GnRH analogue was offered for adequate time for decision making and defer of surgery during school holiday. 5 months after the treatment, hoarseness of voice improved, and phallus reduced to 3cm in length and 1.3cm in width.

P3-246

An Adolescent Girl Presented with Hoarseness of Voice

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The girl was born full-term vaginally with birth weight 3.380kg. She had stayed in neonatal unit for 3 days for neonatal fever. Physical examination was unremarkable. She had normal-looking female external genitalia. She was discharged after a negative infection screen.

She presented again at the age of 11 years with hoarseness of voice. Physical examination revealed normal growth and blood pressure. She had hoarseness of voice with mild laryngeal prominence. She had no goitre and no hirsutism. Pubertal examination showed stage 1 breast, prominent phallus measured 3cm in length and 2cm in width, bilateral palpable gonads in inguinal regions and stage 3 pubic hair. Both labia majora and minora were seen. Urethral opening was seen but vaginal opening was not well seen. Other systemic review was unremarkable.

Extensive investigations were performed for her virilization. Karyotype was 46, XY. SRY gene was present with no mutation detected by Sanger sequencing. Biochemistry showed LH 33.1 IU/L, FSH 61.3 IU/L, oestradiol 26 pmol/L, testosterone 8.3 nmol/L, 17-hydroxyprogesterone 1.9 nmol/L, androstenedione 1.1 nmol/L, AMH 0.39 µg/L, AFP 2 µg/L and b-HCG <1 IU/L. USG scan showed normal adrenal glands, no urogenital anomalies, no uterus and ovary identified and both gonads in inguinal regions.

P3-247

Turner's syndrome mosaicism 45X/47XXX with iron deficiency anemia due to menometrorrhagia

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Turner syndrome(TS) is a chromosomal disorder which occurs in 1/2500 - 1/3000 among female live births, characterized by short stature, pubertal failure and cardiac defects. Mosaicism of 45X/47XXX is extremely rare and accounts for 1.7% of the TS cases. TS with 45X/47XXX is more likely to have spontaneous puberty. The case we present herein is a 13-years old girl who was admitted to Chuncheon sacred heart hospital due to severe anaemia. She was diagnosed with Turner syndrome with karyotype of 45X/47XXX at 4 years of age. She had no dysmorphic trait exception for short stature and no cardiac problems. She had spontaneous menarche at the age of twelve and menometrorrhagia. In the laboratory analyses, severe iron deficiency anemia (hemoglobin, 4.6g/dL; MCV, 56.2fL; iron, 8µg/dL; Transferrin saturation, 1.6%; ferritin, 2.2 ng/ml) was found. Pelvic ultrasound examination revealed normal ovaries and uterus. She transfused packed RBC 500ml and started to take iron supplement. After 3months, hemoglobin and ferritin level were normalized. In patients with 45X/47XXX, attention should be paid not only to the pubertal progression but also to the menstruation – related problems, which improve the quality of life and could prevent future problems that may arise during adolescent.

P3-248

Difficulties in diagnosing variable disorders of sexual development

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Introduction: Disorders of sexual development (DSD) include etiologically heterogeneous group of patients that have disorders of genital development. Consensus guidelines that are currently used, divide all DSD in three main groups - sex chromosomal abnormalities, XX or XY DSD, all divided in subgroups in dependence of genetics and hormonal tests. The phenotypic spectrum of external genitalia, gonads and development of Wolfian and Müllerian duct derivatives varies in all patients. Many syndromic cases stayed unclassified and without easily reached etiology.

Materials and Methods: We describe ten patients with DSD. All patients have ambiguous genitalia with different Prader staging. Phenotypic recognition, imaging, as well as karyotypic, hormonal and biochemical tests were evaluated in all. Six of them had XY and the remaining four had XX karyotype. Additional anomalies were found in 3 patients where syndromic condition was detected.

Discussion and Conclusions: The diagnosis of represents one of the conditions in the neonatal period that need urgent diagnosis and in some cases, early treatment. In some cases the condition stayed undetected till puberty. Clinicians often face many difficulties in performing and providing all necessary genetic and laboratory tests. Clinical workout and diagnostic evaluation paths were constructed in order to facilitate gender assignment in infants as soon as possible. Some of the investigations are not easily available, they are time-consuming, also some conditions still don't have proven molecular defect. Advances in identification of the molecular and hormonal defect, as well as multidisciplinary approach improved the medical care, psycho social and ethical issues in patients with DSD.

Thyroid

P3-249

Association of Subclinical Hypothyroidism and Dyslipidemia in Children and Adolescents

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Background: Subclinical hypothyroidism (SH) is defined as elevated TSH levels while T4 or FT4 levels are normal. In adults, Subclinical hypothyroidism has been correlated to higher levels of total cholesterol, LDL, non-HDL, TG and lower levels of HDL.

Correlation of higher levels of TSH and dyslipidemia in children is controversial. As a result, we designed the study to assess the relation between lipid profile components and TSH levels in children and adolescence.

Method: This cross-sectional study was performed in a growth assessment clinic in Shiraz. Children aged between 2 to 18 years that came to the clinic for routine growth assessment follow up from January till April 2018 were considered. 847 children including 366 boys and 481 girls were included. Subjects were divided into two age groups: 2-9 and 10-18 year olds. TSH levels equal or above 5 and lower than 10 mIU/mL with normal FT4 were considered as subclinical hypothyroidism.

Results: 666 children were euthyroid while 181 had subclinical hypothyroidism. Mean TC in euthyroid children was 160.50 ± 29.070 mg/dl and in SH group 161.39 ± 28.694 mg/dl ($P=0.713$). Mean LDL-C in euthyroid children was 90.96 ± 24.996 mg/dl and in SH group 89.10 ± 23.852 mg/dl ($P=0.369$). Mean HDL-C in euthyroid children was 47.94 ± 10.560 mg/dl and in SH group 49.04 ± 10.361 mg/dl. ($P=0.211$). Mean non HDL-C in euthyroid children was 112.56 ± 27.696 mg/dl and in SH group 112.35 ± 28.136 mg/dl. ($P=0.929$). Mean TG in euthyroid children was 104.98 ± 54.934 mg/dl and in SH group 113.83 ± 91.342 mg/dl. ($P=0.215$). There was no significant difference in mean serum TChol, LDL, HDL, non-HDL and TG levels between euthyroid and subclinical hypothyroid children and in their respective 2-9 and 10-18 year old subgroups. There was no significant difference in prevalence of any of the lipid profile dyslipidemias between euthyroid and subclinical hypothyroid children and in the subsequent age related subgroups. Adjusted for age, gender and BMI Z-score, no correlation was seen between TSH levels and any lipid profile component. ($r=0.033 P=0.331$ for TChol, $r=0.015 P=0.657$ for LDL-c, $r=0.039 P=0.257$ for HDL-c, $r=0.020 P=0.554$ for Non-HDL-c and $r=0.019 P=0.584$ for TG)

Conclusion: By comparing the results of this study with other studies, it is evident that lipid disorder in subclinical hypothyroid children does not have a specific pattern.

P3-250

Evaluation of Clinical, Demographic Data and Treatment Results of Cases with Graves' Disease

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Introduction: Graves' disease is the most common cause of hyperthyroidism in children and adolescents, characterized by development of stimulant antibodies against thyrotropin (TSH) receptors. Environmental and genetic factors are thought to be responsible in triggering autoimmunity.

Materials and Methods: Twenty-nine cases, with Graves' disease diagnosed in Pediatric Endocrinology clinic between January 1999 and December 2018, were included in the study. Patients demonstrating high free T3 or T4 levels and suppressed TSH levels with either thyrotropin receptor antibodies (TRAb) positivity or

requirement of antithyroidal treatment for more than 1 year despite absence of TRAb were diagnosed as Graves' disease. Clinical, demographic features, physical examination findings, laboratory, imaging, treatment processes were obtained from patient files retrospectively.

Results: The median age of the patients included in the study was 13.72 years (1.92-16.68) (82.8% female, 62.1% pubertal). At the time of diagnosis, the median weight, height and body mass index SDS values were -0.4, 0.2, and -0.2, respectively. The most frequent complaints were palpitation (55.2%), sweating (55.2%), weight loss (41.4%), irritability (34.5%), and tremor (34.5%). The duration of symptoms before diagnosis was 1.75 (1-12) months, and the family history of thyroid disease was present in 72.4% of cases. Goiter was found in 55.2% of patients and exophthalmos 17.2%. In laboratory tests, TRAb was positive in 84.6% of the cases and the median values of TSH, fT3 and fT4 were found to be 0.01 μ IU/mL (N: 0.38-5.33), 12.32 pg/mL (N: 2.5-3.9), 3.8 ng/dL (N: 0.5-1.51), respectively. Propylthiouracil treatment was started in 44.8% of the cases and methimazole 55.2%, and also propranolol treatment was added in 86.2% of patients due to tachycardia. In the follow-up, a raise in transaminase levels (maximum of 5 folds) was detected in 3.4% of the patients. The median follow-up period was 30 months, the remission rate was 13.8% and the median time to remission 18.5 months. There was no relapse in any of the patients who had remission. Total thyroidectomy was performed in 24%, and ablation with radioactive iodine was applied to 4% of the cases who were not in remission.

Conclusion: In this study, the majority of cases with Graves' disease were diagnosed after typical clinical findings of hyperthyroidism in pubertal period and the remission rate was found to be consistent with the literature. In addition, anti-thyroid treatment was found to be reliable in the pediatric age group and none of the cases had serious adverse effect.

P3-251

A case of Graves disease with negative thyrotropin stimulating antibodies in a pediatric patient with type 1 diabetes

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Background: Graves disease (GD) is an autoimmune condition caused by direct stimulation of the thyroid epithelial cells by thyrotropin (TSH) receptor antibodies (TRAb). The action of TRAb can be stimulating, blocking or neutral. Antibodies with agonist action are also called thyroid stimulating immunoglobulins (TSI). The diagnosis of GD is typically confirmed with TSI titer which is positive in >90% of patients. In patients that have negative TSI, highly sensitive and specific assays for detecting TRAb antibodies are available but they are rarely ordered.

Clinical Case: The patient is a 14-year male with type 1 diabetes mellitus that was found to have a suppressed thyroid stimulating hormone (TSH) <0.002 μ U/mL(0.350-4.94), elevated free thyroxine (FT4):1.8 ng/dL(0.7-1.5) with elevated total triiodothyronine (T3):1.9 ng/dL(0.6-1.6), negative thyroid-stimulating immunoglobulin (TSI) <89(<140%), positive

antithyroid peroxidase antibodies (antiTPO) -50.4IU/mL (0.0-5.6) and positive anti-thyroglobulin antibodies-43.2IU/L (0.0-4.1). Based on these studies he was diagnosed with hyperthyroidism due to Hashimoto thyroiditis.

Initially, he was asymptomatic and he was not placed on any antithyroid medication. Two months later due to weight loss and elevated FT4-2.0 ng/dL, he was started on methimazole (MMI) 2.5 mg daily, adjusted to 5mg daily. Seven months after starting MMI, FT4 had normalized. He developed neutropenia and MMI was discontinued. One month later, FT4 increased to 2.1ng/dL and T3 -2.1 ng/dL, TSI negative and TRab: 6.93 IU/L (0.00 -1.75). He was diagnosed with hyperthyroidism due to GD. The decision was made to restart him on MMI and propranolol. We consulted hematology-oncology regarding his mild neutropenia, and it was thought that most likely it was due to ethnic variation. An anti-neutrophil antibody level was obtained and was negative. Parents discontinued propranolol and were not comfortable with a higher dose of MMI. Currently, he is on low dose MMI 5mg daily and his FT4 continues to be elevated. Permanent treatment for his autoimmune hyperthyroidism has been discussed with family.

Discussion: This was an interesting case of TSI negative, TRAb-positive Graves disease in a patient with type 1 diabetes. Initially, his hyperthyroidism was thought to be due to Hashitoxicosis, based on his clinical presentation and laboratory studies. When his hyperthyroidism was not improving TRab was measured and was positive. Widely available TRAb measurement methods have been significantly improved recently. However, TRAb is not always used in the United States as a first-line test in the differential diagnosis of hyperthyroidism.

P3-252

An unusual presentation of Hypothyroidism: Van Wyk-Grumbach syndrome

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Introduction: The association of juvenile hypothyroidism, precocious puberty and ovarian enlargement is known as Van Wyk and Grumbach syndrome (VWGS). This diagnosis is considered on the basis of imaging findings and thyroid function analysis.

Case Report: Herein we report a case of 9 years old girl was referred to the endocrinology department with a suspicion of precocious puberty after having progressive breast enlargement and premature menarche. Upon physical examination, her height was 91.5 cm (< -4SDS), with weight of 24 kg (-1 SDS). She had a puffy face with yellowish discoloration and very dry skin, and her thyroid gland was normal on palpation. On pubertal assessment, her breasts were Tanner stage 3 and pubic hair was Tanner stage 1. Hormonal investigations revealed elevated thyroid-stimulating-hormone (TSH) (>150 μ UI/ml) and low Free-thyroxine. Follicle-stimulating-hormone level was 7.5 mUI/ml, Luteinising-hormone (LH) level was < 0.07 mUI/ml (0.1-6.0) and prolactin circulating level were normal. Thyroid-peroxydase antibodies were elevated. Abdominal ultrasound was normal with normal appearance of the uterus, ovaries and no visible endometrial line. X-ray of the

wrist revealed a delayed bone age. Ultra sonography of the thyroid showed a heterogeneous highly suggestive for thyroiditis. Brain magnetic resonance imaging (MRI) showed an enlarged pituitary gland, with homogeneous enhancement.

The diagnosis of ovarian hyper stimulation secondary to severe hypothyroidism was made and thyroid hormonal replacement was started on levothyroxine, increased gradually to 175 µg (7µg/Kg/day). Upon follow-up, 2months after starting on treatment, she reported significant improvement of clinical features of hypothyroidism and there was a significant involution of her breast tissue.

Repeat laboratory tests 6 months later showed normalisation of TSH and pituitary MRI 10 months after thyroid replacement therapy, showed a reduction in the size of the gland.

Conclusion: This case demonstrates that VWGS should be kept in mind even in patients without cystic ovarian enlargement. The mechanism of VWGS is not yet clear, multicystic ovaries and hyperfunction may result from elevated levels of circulating FSH. It is also possible that increased sensitivity of the ovaries to the circulating gonadotropins could result from the hypothyroid state directly or via increased prolactin. In patients with isosexual pseudo-pubertal precocity, early recognition of this diagnosis and initiation of thyroid hormone replacement can avoid further diagnostic procedure and unnecessary surgery. It helps to resolve symptoms and improve final height.

P3-253

Child thyrotoxicosis Syndrome: Structure and Characteristics

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Objective: To study the structure and characteristics of child thyrotoxicosis syndrome.

Materials and Methods: At the 1st stage, medical records of patients treated at the Endocrinology Unit of the Children's Hospital named after Z.A. Bashlyeva of the City of Moscow in 2014-2018 (n=4530) were analyzed. At the 2nd stage, a primary examination of 106 children 3 to 17 years old with a diagnosis of thyrotoxicosis syndrome was performed. Serum TSH, free T4, anti-thyroglobulin, -thyroid peroxidase and -TSH receptor antibodies were analyzed in all patients; ultrasound examination of thyroid gland as well as thyroid gland scintigraphy (n=4) and molecular genetic PCR assay with direct sequencing (n=2) were performed as well. Immunological criterion of Graves disease was defined as anti-TSH antibodies values > 1.75 IU/mL.

Results: Thyrotoxicosis syndrome accounted for 2,3% in the structure of endocrine diseases in children. All the cases were presented with an overt clinical form of the disease. Thyrotoxicosis syndrome was significantly more frequently diagnosed in girls (81,1%) as compared to boys (18,9%, p=0.000) and was more frequent in teenagers (85,8%) as compared to prepubertate age children (14,2%, p=0.000).

Immunogenic forms of thyrotoxicosis syndrome in children were diagnosed in 94,3% of the cases and were represented by Graves disease (87,8 %) and thyrotoxicosis phase of autoimmune thyroiditis (6,6%, p=0.000).

Non-immune forms of thyrotoxicosis were significantly less frequent, 5.6% (p=0.000) and were represented by the following nosologies: single-node toxic goiter – 1.9% (2/106), iodine-induced thyrotoxicosis – 0.9% (1/106), multinodular toxic goiter in 0.9% (1/106), thyrotoxicosis due to TSHR gene activating mutation in 0.9% (1/106), drug-induced thyrotoxicosis in 0.9% (1/106).

Conclusion: The structure of thyrotoxicosis syndrome is heterogeneous, including both immune and non-immune forms; this should be kept in mind when considering the diagnostic work-up plan and the choice of the treatment strategy.

P3-254

Encephalitis associated with autoimmune thyroiditis: a rare cause of encephalopathy in children

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A ten year old girl was brought by the emergency mobile service for a persistent status epilepticus despite administration of Diazepam on site. She had presented headaches for the last three days and one episode of fever was suspected but not measured four days earlier. She had one episode of dizziness five days earlier.

Persistent status epilepticus required invasive ventilation as well as deep sedation with Levetiracetam, Midazolam, ketamine, phenytoin, valproic acid and frisium.

Biological assessment, brain scan and bacteriological and viral cerebrospinal fluid (CSF) analysis were normal. Magnetic resonance imaging of the brain showed a vasogenic oedema. The initial search for autoimmune antibodies on CSF was negative. Moderate hypothyroidism with high anti-TPO antibodies was noticed. Thyroid ultrasound confirmed the appearance of thyroiditis. Because of a likely autoimmune etiology, a high-dose corticosteroid therapy was introduced followed by plasmapheresis which lead to clinical improvement.

Hashimoto encephalitis is also known as Steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT). The estimated prevalence is 2.1 per 100 000 and is relatively rare in paediatric population. Association of acute encephalopathy with elevated antithyroid antibodies after exclusion of other etiologies (infection, tumor, toxic, metabolic) suggests the diagnosis. Most pediatric patients present with slowly progressive encephalopathy with epileptic seizures as the most common symptom (60–80%) which require intensive treatment in order to limit brain damage.

Thyroiditis is noticed with increased anti-thyroglobulin and / or anti-thyroperoxidase antibodies. It appears that thyroid antibodies are not directly responsible for brain damages, and the abnormalities in thyroid hormone levels are generally too mild to explain the brain disease. Other auto-immunue encephalopathies in children are associated with other autoantibodies, such as anti-NMDAR or GABA-B-R.

The standard treatment consists in a systemic corticosteroid therapy and/or plasma exchange, while other lines of immunotherapy are sometimes needed. Antithyroid antibody titer can be used to predict responsiveness to treatment in the acute stage, but cannot be used as a marker of relapse.

P3-255

Association of BMI Z-score and Subclinical Hypothyroidism in Children and Adolescents

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Background: Subclinical hypothyroidism is defined as elevated TSH levels while T4 or FT4 levels are normal. Elevated TSH levels are linked with obesity in adults. In a recent meta-analysis in Iran, 6.1% of children below 18 had obesity. Due to the low number of studies on the subject in children we, designed the study to assess the relation between BMI Z-score and TSH levels in children and adolescence.

Method: This cross-sectional study was performed in a growth assessment clinic in Shiraz. Children aged between 2 to 18 years that came to the clinic for routine growth assessment follow up from January till April 2018 were considered. 850 children including 365 boys and 485 girls were included. Children with TSH between 0.3 and <10 mIU/L and normal free T4 (0.8-1.8 ng/dL) were included in the study. Participants with drugs or diseases affecting serum lipid or thyroid hormones were excluded. TSH levels equal or above 5 were considered abnormal. All participants with high TSH levels were considered for a second remeasurement. For these participants, second TSH levels were considered for the study. BMI Z-score was calculated by the LMS (lambda, mu, sigma) method based on the reference of BMI distribution of CDC growth charts. 141 participants were defined as underweight below 5th percentile (<-1.65 BMI Z-score), 369 as healthy weight between 5th and 85th percentile (-1.65 – +1.04 BMI Z-score), 116 as overweight between 85th and 95th percentile (+1.04 – +1.65 BMI Z-score) and 224 as obese above 95th percentile (>+1.65 BMI Z-score).

Results: Prevalence of subclinical hypothyroidism is increased in higher BMI groups. 9.9%, 13.8%, 17.2% and 20.5% of underweight, healthy weight, overweight and obese had subclinical hypothyroidism respectively. Obese and overweight participants had higher odds of subclinical hypothyroidism than those who were not (OR: 1.649, P=0.010, CI95% 1.126 – 2.413). On the other hand, Subclinical hypothyroid participants had higher odds of overweight or obesity than those who were euthyroid (OR: 1.650, P=0.010, CI95% 1.128 – 2.413). When TSH is set as a dependent value, TSH level is increased ($\beta=0.126$, $r=0.125$, $P=0.001$) with an increase in BMI Z-score. When BMI Z-score is set as a dependent value, BMI Z-score is increased ($\beta=0.113$, $r=0.243$, $P=0.001$) with an increase in TSH level.

Conclusion: BMI Z-score and Subclinical hypothyroidism are positively correlated however studies should be performed on establishing the causality.

P3-256

Pseudoprecocious Puberty in a Girl with Untreated Acquired Hypothyroidism

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Background: Hypothyroidism is associated with impaired growth and pubertal delay. However, there are female patients with untreated acquired hypothyroidism and paradoxical precocious pubertal signs, which include thelarche, galactorrhea and menarche. These girls do not have axillary and pubic hair development. The exact mechanism for this pseudoprecocious puberty is not clear. The most probable explanation is that high levels of TSH act through the FSH receptor and cause gonadal stimulation.

Clinical Case: A 10-year old girl was admitted to Endocrinology department with complaints of short stature, fatigue, loss of appetite, constipation and cold intolerance. Physical examination showed: pale and dry skin, puffy face, height 123 cm (<3rd percentile), body weight 22 kg (<3rd percentile), blood pressure - 88/56 mmHg, pulse 59 beats/ min. Thyroid gland was not tender but the size was normal. Breast development was Tanner stage III – IV without galactorrhea or other pubertal signs. Bone age was 7 years and 10 months. Laboratory data showed: Haemoglobin-10.5 g/dl, Cholesterol- 7.02 mmol/l (normal <4.40), Tryglycerides 1.5 mmol/l. Hormonal evaluation revealed: FT4- <4.50 pmol/l (normal 10.8 – 22.7), TSH 1261 mIU/l (normal 0.40-4.00), Anti-Thyroglobulin Ab- 676 IU/ml (normal <35), Anti- Thyroid Peroxidase Ab 553 IU/ml (normal <40), pubertal levels of FSH and prepubertal levels of LH and prolactin. Ultrasound of the thyroid showed typical changes for autoimmune thyroiditis. Echocardiogram revealed moderate pericardial effusion. Initial treatment was with increasing doses of L-Thyroxin and decreasing doses of corticosteroids. Follow up showed improvement of patient's physical condition and hormonal status, as well as decrease in the size of her breasts.

Conclusion: Early recognition of thyroid dysfunction is very important because untreated hypothyroidism has negative effect on growth and metabolism and may also cause pseudoprecocious puberty in girls. Hormonal replacement with L-Thyroxin leads to a resolution of all these complications.

P3-257

Bilateral Hip Pain as First Symptomatic Expression of Severe Primary Hypothyroidism

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Introduction: Legg-Calvé-Perthes disease is an idiopathic osteonecrosis of the femoral head with uncoupling of bone resorption and formation, presenting as unilateral involvement in most children. Symmetric involvement suggests other conditions: skeletal dysplasia, osteonecrotic entities including hypothyroidism, Gaucher's disease, glycogen storage defects, sickle cell anemia.

Case Presentation: We present a case of bilateral hip pain with symmetrical fragmentation and flattening of the femoral head caused by a severe acquired hypothyroidism.

A 14-year-old boy presented with insidious bilateral hip pain and limp and no associated systemic symptoms. He denied any trauma or infection. He had no significant medical or surgical history and took no treatment. He was developmentally normal and played football. Family history was noncontributory.

In the Emergency Department the diagnosis of Legg-Calvé-Perthes disease was made. On the second physical examination, we noted a short stature (131 cm, - 5 SD) without dysmorphic features or body disproportions. The patient had bilateral limited internal/external rotation and abduction. He walked with an antalgic gait. His neck was supple with no palpable thyroid. His pubertal stage was Tanner V. The rest of the somatic exam was unremarkable.

Laboratory evaluation revealed severe primary hypothyroidism: TSH (thyroid-stimulating hormone) 312 mIU/mL (0.46 – 4.7), T4 (thyroxine) 2.4 pmol/L (9 - 28), T3 (triiodothyronine) 2.95 pmol/L (4.3 – 8.1), thyroglobulin 7.4 µg/L (1.4 - 78) with absent antithyroglobulin and antithyroperoxidase antibodies. IGF1 (insulin-like growth factor 1) and IGFBP3 (insulin-like growth factor-binding protein 3) levels were also low, without growth hormone deficiency. The hematologic and lipid profile, hepatic and renal function, were normal.

Radiological investigations showed atrophic thyroid tissue on ultrasound, delayed bone age (10 years) along with bilateral symmetrical femoral head fragmentation and collapse. No other skeletal abnormalities were found.

Thyroid hormone replacement (L-thyroxine, 5 µg/kg/d) induced rapid growth (height velocity 26 cm/20 months), accelerated skeletal maturation with progressive improvement in gait and hip pain relief.

Conclusion: The differential diagnosis of hip pain in childhood includes many inflammatory and infectious causes that are usually heralded by unilateral hip pain.

Bilateral symmetric involvement with femoral head fragmentation and collapse, in association with short stature, is an important clinical clue suggesting a systemic disease like thyroid-related skeletal disorder.

Thyroid hormones exert anabolic actions on the developing skeleton, influencing chondrocytes, osteoblasts and osteoclasts activity and have catabolic effects in adulthood.

P3-258

The challenge to treat neonatal autoimmune hyperthyroidism in a small preterm

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Background: The prevalence of hyperthyroidism in pregnancy is about 0.2%, mostly due to Graves disease. Neonatal autoimmune hyperthyroidism caused by the transplacental passage of stimulatory thyrotropin receptor antibodies (TRAB) of the IgG class is a rare disorder. It occurs in only 2% of the neonates of

mothers with Graves disease, is transient and associated with high morbidity and mortality rates up to 25%. Antithyroid drugs are the treatment of choice for neonates and preterm neonates with hyperthyroidism.

Case Report: We report the rare case of a preterm neonate born at 28+5 weeks of gestational age with a birth weight of 1580 g. After a few days the boy became irritable and developed tachycardia. At the 6th day of life the laboratory investigations revealed hyperthyroidism with suppressed serum TSH-levels, elevated fT4-levels and positive TRABs. Under treatment with propranolol and methimazole the fT4 serum levels declined to the lower limit of the normal range, so that an additional supplementation with levothyroxine was initiated. Methimazole was stopped after 3 months when TRABs were negative. The TSH serum levels remained very low for 6 months while fT4 was constantly in the normal range under treatment with levothyroxine. Eventually the levothyroxine dose was reduced and the patient became euthyroid without treatment. Serious side effects under treatment with methimazole such as neutropenia or elevated liver enzymes did not occur.

Conclusions: Although neonatal hyperthyroidism due to maternal TRABs is rare, thyroid function has to be monitored in all neonates born from mothers with Graves disease. Once hyperthyroidism is diagnosed antithyroidal treatment has to be started. Prematurity is not a contraindication for the use of antithyroidal drugs. The treatment has to be monitored thoroughly because of the known serious side effects. Furthermore, the fT4 serum levels can decline rapidly in preterm neonates and additionally the serum TSH levels remain suppressed for months. To avoid hypothyroidism intermediate treatment with levothyroxine is important.

P3-259

Graves' disease in a 3 year-old patient with agranulocytosis due to methimazole

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Introduction: Graves' disease is the most common cause of hyperthyroidism in children with autoimmune thyroid disease. Clinically, goiter, tachycardia, restlessness, craniosinostosis, hyperactivity, growth retardation, diarrhea may occur. Graves' disease is rare under 4 years of age. Treatment options include antithyroid therapy, surgery, and radioiodine therapy. The most commonly used antithyroid therapy is methimazole and has serious side effects such as hepatitis, neutropenia and agranulocytosis.

Case: The patient was 3 years and 2 months old girl, was referred to the external center for restlessness. She had no additional complaints. She was born term 2800 gr. In her past medical history, there was no thyroid disease, but she was being followed up by pediatric neurology and genetics because of microcephaly, growth retardation. In her physical examination; weight:10,2 kg (-2,81 SD), height:86,8 cm (-2,48 SD), thyroid was nonpalpable, puberty was Tanner stage 1, heart rate 125/ min, BP: 100/60 mm/Hg. Laboratory results:fT3:7,78 pg/ml, fT4: 2,79 ng/dl, TSH: <0,005 uIU/ml, anti Tg:0, Anti TPO: 33,9 IU/ mL, Thyrobulin:42,85 TSH receptor antibody:8,2 U/L (N=0-14), urine iodine:145,4 ug/L.

In her thyroid ultrasound, it was heterogeneous. In thyroid scintigraphy, thyroid gland is in normal location, there is a slight increase in the size of the gland.

1 mg/kg propranolol and 0.5 mg/kg/day metimazole treatment were started. At 4th month of treatment, she was admitted to emergency polyclinic with fever complaint. Her physical examination was normal but in CBC, WBC 1700 uL, ANC 800 uL. She was evaluated by pediatric hematology. Her viral markers were negative. Methimazole was discontinued because of its side effect. On the 20th day of her follow-up, her hemogram returned to normal, she was hyperthyroid again (sT3: 4.7 pg/ml, sT4: 1.46 ng/dl, TSH: 0.051 uIU/ml, thyroglobulin: 26 ng/ml TSH receptor ab: 23.73 U/L) and methimazole treatment was started. In the last follow-up visit, the patient's thyroid function tests, euthyroid and hemogram were normal.

Conclusion: Graves' disease is the most common cause of hyperthyroidism in childhood and it is rarely seen in children under 4 years of age. Antithyroid therapy, which is the first treatment option, has a serious complication such as agranulocytosis. It is usually dose dependent and can be seen within the first 6 months after the treatment and it is most common in the first 3 months. Patients should be closely followed because of the risk of agranulocytosis, if necessary, a different treatment option such as thyroidectomy or radioiodine therapy should be tried.

P3-260

Hashimoto's Thyroiditis in children: Case series report of three patients

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Hashimoto's thyroiditis (HT) is most commonly caused by autoimmune thyroid disease and rarely in children. It is characterized clinically by gradual thyroid failure, with or without goiter formation, due to autoimmune-mediated destruction of the thyroid gland involving apoptosis of thyroid epithelial cells. In fact, thyroid function at presentation may significantly vary in the different pediatric reports, ranging from euthyroidism (52.1%) to overt hypothyroidism (41.4%) or, occasionally, hyperthyroidism (6.5%).

Objectives: To describe the clinical and laboratory features, as well as the management of patients with Hashimoto's disease at Vietnam National Children's Hospital (NCH).

Subjects and Methods: This is case series study including clinical features, biochemical, image findings, and management of 3 children (2 girls and one boy) with HT.

Results: All three exhibited the typical symptoms and signs of enlargement forming a painless goiter. The first patient is a third child of the family who is 7 years old, with a history of normal motor and mental development. She presented with diffuse goiter grade 3 and difficult swallowing; investigations showed low levels of plasma T3 (0.6 nmol/l) and FT4 (4.39 pmol/l), elevated level TSH (117.51 mIU/l), Anti-TG (1748 U/ml), Anti-TPO (339.6 U/ml); thyroid ultrasonography showed hypertrophy, uniform parenchyma and no focal nodule. The second patient is an 8-year-old girl. Her painless

goiter was recognized from two weeks, investigations showed low levels of plasma T3 (0.89 nmol/l) and FT4 (4.19 pmol/l), elevated levels of TSH (129.7 mIU/l), Anti-TPO (>7260 U/ml), Anti-TG (2547 U/ml) and normal levels of TRAb (< 0.3 U/l); echocardiography was normal but manifesting sinus arrhythmias on the electrocardiogram. The last patient was a 6-year-old boy, he presented with goiter grade IIa and normal function of thyroid during first year of his illness. The review data showed FT4 = 12.91 pmol/l, TSH 23.44 mIU/l, Anti-TG 2073 U/ml, hypertrophic thyroid on ultrasound. All three patients are treated with thyroid hormone replacement - levothyroxine.

Conclusions: three cases with HT were confirmed diagnosis in a week at refferal center, with the manifestations of goiter and hypothyroidism. This implies that whether or not all goiter patients are tested for autoimmune thyroid marker.

P3-261

Mutation of RET gene causes multiple endocrine neoplasia type 2B in an Adolescent: report of one case and literature review

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Objective: To summarize the clinical features and genetic characteristics of a patient with multiple endocrine neoplasia type 2B (MEN2B) and to review the literatures.

Methods: We summarized clinical features, gene sequencing result, treatment and prognosis of a child suffered with MEN2B who was admitted to the Department of Pediatrics, Ruijin Hospital, Shanghai Jiaotong University School of Medicine in February 2016. And we also searched for relevant cases through the medical literature databases such as Pubmed, Wangfang and so on in order to generalize characters of this rare disease.

Results: The patient had difficulty in defecation soon after birth. Neck masses were noticed when she was 9 and grew progressively. Multiple neuromas were found in the gums, tongue and cheek mucosa when she was admitted in our hospital at the age of 12. Many hard nodules were palpable in her thyroid. Serum calcitonin level was significantly elevated. Bilateral thyroid cancer with cervical lymph node metastasis was suspicious when using ultrasound. Next-generation sequencing showed the proband had a heterozygous mutation in RET proto-oncogene (c. T2753C; p. M918T). Then thyroid cancer extended radical mastectomy + radical neck dissection were performed in her. Bilateral medullary thyroid carcinoma (MTC) was verified by thyroid pathology. 6 months after the first operation, she was taken mediastinal lymph node dissection because of mediastinal metastases occurring. Calcitonin was still higher than normal in the current follow-up. MEN2B was very rare and only 20 cases have been reported in China. Few was diagnosed during childhood.

Conclusion: Hirschsprung disease with thyroid mass is a clue to screen MEN2B, which is caused by RET mutation. Certain mutation (p. M918T) can cause MTC definitively.

P3-262**A 12 year old boy with multifocal papillary thyroid carcinoma**

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Thyroid carcinoma in pediatric patients usually manifests as an asymptomatic neck mass, with a reported incidence of cervical lymphadenopathy that ranges from 35-83%.

Multifocal involvement of the thyroid gland is a well-recognized feature of papillary carcinoma. The reported frequency is about 20%, with wide variations depending on the extent of the sampling and reporting by the pathologist

A 12 year old boy presented with the 2 months history of increased thyroid gland, hoarse voice.

There was no family history of thyroid cancer and no history of irradiation.

Physical Examination. there was significant bilateral cervical lymphadenopathy and thyroid gland was palpable and firm.

Laboratory Examination. Routine blood examination and the level of thyroid hormone were normal.

Ultrasound scan of thyroid showed typically location of the gland with no additional lesions. The thyroid gland is mildly hypo-echogenic. The echo-structure is not homogenous due to the small and large hyper-echogenic lesions. Regional lymph nodes are visualized in the regions: right and left submandibular, jugular area, from 3 up to 9 mm, plural. The tissue of the lymph nodes is hypo-echogenic. Echo-structure is heterogeneous due to areas of fibrosis and cystic degeneration.

Total volume by Brunn method (cm³): 42.67. Right lobe - 20.35 (47.7%); the left lobe is 22.32 (52.3%).

Ultrasound scan of abdomen and chest X-ray had no significant abnormality.

Fine needle aspiration cytology was performed from the middle third of the left lobe of the thyroid gland with a diameter of 16 mm and left submandibular lymphnode 9 mm. Cytological diagnosis of papillary thyroid carcinoma with metastasis to the lymph node was made (BSRTC: VI. Malignant).

Total thyroidectomy with bilateral neck dissection was done.

Histological examination. Multifocal papillary thyroid carcinoma (pTm3aN1b L1 V0 Pn0 R1).

Tumor cells are localized in both lobe (subtotal substitution of the tissue of both lobe by the tumor). There are signs of tumor invasion in perimysium of skeletal muscle. Three lymph nodes with carcinoma metastases were found near to the tissue of both particles of fatty tissue.

P3-263**Papillary Thyroid Cancer in Children: Single Center Results**

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Introduction: Thyroid cancers are rare cancers in children and their incidence is 1.4% in pediatric malignancies. However, its frequency is increasing. While the incidence of prepubertal children is equal among girls boys, it increases with age in female patients. Radiotherapy, which is applied to the neck region, and hashimoto disease are the risk factors. The relationship between Hashimoto's disease and papillary thyroid cancer is thought to be associated with chronic inflammation. The prognosis is very good when appropriate treatment is applied. Most patients are diagnosed with thyroid nodules or neck lymph nodes. Thyroid ultrasound, fine needle aspiration biopsy and diagnostic hemithyroidectomy are performed. Treatment of total thyroidectomy and lymph node dissection recommended for each patient in recent years. In the presence of lymph node and distant metastases, postoperative iodine 131 is recommended.

The clinical and pathologic features and prognosis of patients with papillary thyroid cancer were analyzed retrospectively.

Cases: The data of 19 patients diagnosed in our clinic were evaluated retrospectively. 14 of the patients were female and 5 of them were male and the mean age at diagnosis was 13.6. The most common complaint was neck swelling. Most patients had neck lymphadenopathy at the time of diagnosis. Five of the patients were diagnosed with thyroid nodules on the basis of hashimoto. In the examination of these patients, nodules were not detected and nodules were detected in the ultrasound examination. When we look at the distribution according to years, it was seen that the number of patients diagnosed with hashimoto increased. The pathology of all patients was consistent with papillary thyroid cancer. All of the patients were operated, except 2, all of them received radioactive iodine treatment after the operation.

Result: In recent years, the incidence of thyroid papillary cancer has increased. In addition, it has been observed that patients diagnosed with hashimoto have also increased in patients diagnosed in recent years. Therefore, we would like to emphasize the importance of performing an annual ultrasound scan of hashimoto thyroiditis.

P3-264

Cardiac Tamponade Associated with Hypothyroidism in Rwandan Child

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We report a case of a child who presented with huge pericardial effusion complicated to cardiac tamponade secondary to primary hypothyroidism. Due to the severity of cardiac tamponade, pericardiocentesis was performed to relieve the compression effect. The child improved with Levothyroxine treatment.

Hypothyroidism is a rare cause of pericardial effusion in children. If the pericardial effusion increases in volume, cardiac tamponade with clinical manifestations can result. The pericardial fluids may be rich in proteins and cholesterol. Treatment with thyroxine therapy can improve outcomes.

Case Report: A three year old male presented to University Teaching Hospital of Butare (CHU Butare), Rwanda with a one month history of shortness of breath and lower limb edema. The physical examination revealed an acutely ill child in respiratory distress with tachypnea of 52 cycles per minute. Suprasternal, intercostal, and subcostal recessions were also observed. Crackles and distant heart sounds were heard on auscultation. The child presented hepatomegaly of 3 cm below costal margin. Both weight and height were in normal age ranges.

The differential diagnoses included congenital non-cyanotic heart disease, pericardial effusion, dilated cardiomyopathy with congestive heart failure, and pneumonia.

Heart ultrasound revealed huge pericardial effusion (4.1 cm) with tamponade effect. Treatment consisted of pericardiocentesis, oxygen therapy, corticosteroid, and diuretics (Furosemide). Pericardiocentesis yielded 550 ml of gold-brown fluid. Fluid bacteriology was negative. Fluid cyto-chemistry was also normal. After 2 days, the child's condition improved. At this point, treatment was continued with Furosemide and Prednisolone only, thinking about pericardial effusion of unknown origin. After 3 weeks, there was a huge pericardial effusion. Pericardiocentesis was again performed and 470 ml of gold-brown fluid was removed. As a result, hypothyroidism was suspected. Thyroid function revealed low T3: 1 pg/ml (normal range 1.4-4.98 pg/ml) and high TSH: 15.857 microIU/ml (normal range: 0.4-7.0 microIU/ml).

The child was given Levothyroxine at 25 mcg per day increased to 50 mcg per day after two weeks. After 3 months, the child had normal thyroid function. T3 was 4.711 pg/ml, T4 was 0.576 ng/dl, and TSH was 1.117 microIU/ml. Heart ultrasound revealed mild pericardial effusion without heart function compromise.

Conclusion: Hypothyroidism is an overlooked etiology of pericardial effusion and cardiac tamponade. Hypothyroidism should be considered in case of massive pericardial effusion without other common causes. Conservative management with thyroxine and thorough monitoring of effusion leads to excellent results. However, emergent pericardiocentesis should be considered in severe cardiac tamponade.

Late Breaking Posters

P3-265

Plasma Asprosin Concentrations Are Increased and Associated with Insulin Resistance in Children with Obesity

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Objective: Asprosin, a novel peptide that has recently discovered as an important regulatory adipokine, is relevant to obesity in animals and adult humans. Little is known about its roles in children. The aim of the current study was to determine the potential role of asprosin and explore its relationship to various obesity-related markers in children with obesity.

Methods: A cross-sectional study was conducted among 119 Chinese children, including 79 children with obesity and 40 lean controls. Anthropometric parameters, clinical data and circulating TNF- α , adiponectin, leptin and asprosin levels were measured.

Results: serum asprosin concentrations were significantly elevated in children with obesity compared with lean controls. Children with insulin resistance had higher asprosin levels than non-insulin resistance group. Asprosin was positively correlated with Waist-to-hip ratio (WHR), diastolic blood pressure (DBP), homoeostasis model of insulin resistance (HOMA-IR), leptin-to-adiponectin ratio (LAR), tumor necrosis factor- α (TNF- α) independent of their body mass index standard deviations score and age. In multivariable linear regression analysis, WHR and HOMA-IR were associated with the expression of asprosin.

Conclusions: serum asprosin are increased in children with obesity and associated with insulin resistance. It may be proposed as a novel marker to predict advanced disease.

P3-266

A Novel Mutation of INSR Gene in a Child with Type A Insulin Resistance

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Background: Mutations of insulin receptor gene (INSR) lead to a wide spectrum of inherited insulin resistance syndromes. Type A insulin resistance is one of the these syndromes which is inherited autosomal dominant and leads to mild clinical symptoms after puberty.

Objective and Hypothesis: To report a novel mutation of INSR gene mutation in a case of Type A insulin resistance who presented with transient neonatal diabetes and then episodes of hypoglycemia and hyperglycemia during childhood.

Case: A full-term Afro-Caribbean female infant, of birth weight 1.89kg, developed transient neonatal diabetes with negative genetic testing (microarray, TNDM 6q methylation analysis). At the age of 2.8 years, she presented with episodes of postprandial and fasting hypoglycemia. Her examination showed satisfactory growth, lipodystrophy, acanthosis nigricans and isolated thelarche. Further investigations demonstrated that the child after 12 hours of fasting developed hypoglycemia (glucose 2.8mmol/L), with inappropriately raised insulin level of 5.4mU/L. Her oral glucose tolerance test (OGTT) showed excessively high levels of insulin throughout the test (>300 mU/L) along with hypoglycaemia (glucose 1.6mmol/L) at 2.5 hours of the test. The mixed meal test also confirmed the diagnosis of postprandial hyperinsulinemic hypoglycemia (PPHH). She had negative genetic analysis for Familial Lipodystrophy (*LMNA* and *PPARG* genes) and Hyperinsulinism (*ABCC8* and *KCNJ11* genes). At the age of 5.1 years she started acarbose treatment for the management of PPHH that lasted for two years. Subsequently, she developed frequent episodes of hyperglycemia along with postprandial and fasting episodes of hypoglycemia recorded persistently on continuous glucose monitoring. Her HbA1c and fasting lipids remained within the normal range. She had continuously suppressed androgens and her pelvic ultrasound showed pre-pubertal appearance of her internal genitalia until the age of 8.7 years. She has normal baseline pituitary function and her LHRH showed predominant FSH response. Treatment of metformin along with carbohydrate diet modification and corn starch started at the age of 7 years not only improved fasting tolerance but also episodes of hyperglycemia and post-prandial hypoglycemia. Genetic testing identified a novel heterozygous deletion of exon 22 in INSR gene.

Conclusion: The present case details the clinical features of a patient with genetically proven Type A insulin resistance. Early age manifestation, neonatal diabetes and also PPHH can be another presentation of this disease. Children with this can be quite challenging to manage using pharmacotherapy and dietary modification. Further accumulation of genetically proven cases and long-term treatment outcomes following early diagnosis are required to understand the dynamics of this disease.

P3-267

Indexes of Adiposity and Body Composition in the Prediction of Metabolic Syndrome In Obese Children and Adolescents: Which Is the Best?

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Objective: There is no agreement about which index of adiposity and/or body composition is the most accurate in identifying the metabolic syndrome (METS). The aim of our study was to compare the accuracy of the different indexes in order to recognize the most reliable.

Study Design: We evaluated 1332 obese children and adolescents (778 females and 554 males), aged 14.4 ± 1.8 yrs., Body Mass Index (BMI) standard deviation scores (SDS) 2.99 ± 0.55 , followed at the Istituto Auxologico Italiano, a tertiary center for childhood obesity. For each subject the following indexes were assessed: BMI, BMI SDS, Fat-Free Mass Index (FFMI), Fat Mass Index (FMI), Tri-Ponderal Mass Index (TMI), Waist-to-Height ratio (WtHR) and a new one, the Body Mass Fat Index (BMFI), which normalizes the BMI for percentage of body fat and the waist circumference. Thereafter we calculated for each index a threshold value for age and sex, in order to compare their accuracy, sensitivity and specificity in identifying the METS.

Results: There was a good correlation among indexes ($p<0.0001$ for all). However, when the area under the curve (AUC) was compared, some of them, in particular the BMFI and the BMI, performed better than the other ones, although the differences were small.

Conclusions: BMI, which neither considers body composition nor fat distribution, performs as good as other indexes, and should therefore be the preferred one, also because of the easiness of its calculation.

P3-268

Clinical, Laboratory and Radiological Assessment of Obese and Non-Obese Girls Evaluated for Early Puberty

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Aim: Although genetic factors are primarily responsible for the etiology of puberty, nutrition and environmental factors are also known to be effective. Obesity is associated with various metabolic complications and affects many aspects of pubertal development such as changes in pubertal hormones and onset of puberty. However, the relationships between these factors are still unclear. It has been reported that overweight and obese children generally have

advanced bone age with accelerated growth and sexual maturation. We aimed to investigate whether there is a difference in terms of clinical, laboratory and radiological findings between obese and non-obese girls who presented with breast development and were examined for early puberty.

Methods: Fifty overweight and obese and fifty normal weight girls (between 3-8 years of age) who were admitted to the pediatric endocrinology clinic for breast development and investigated for early puberty were included in the study. Cases with genetic or hormonal obesity, chronic disease and drug use, laboratory or radiologically diagnosed as central precocious puberty (CPP) due to pituitary or intracranial pathologies and peripheral precocious puberty due to liver, renal, thyroid, adrenal pathologies were excluded from the study. Chronological age (CA), body weight standard deviation score (SDS), height SDS, body mass index (BMI) SDS, bone age (BA), BA-CA difference (Δ BA-CA), basal and stimulated follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) and peak LH / FSH ratio were recorded. Uterine long diameter, uterine and ovarian volumes were evaluated by pelvic ultrasound. CPP was diagnosed when the peak LH levels after gonadorelin stimulation was > 5.0 U/L.

Results: Height SDS and Δ BA-CA values of obese subjects were found to be statistically higher than normal weight controls ($p = 0.001$, $p = 0.02$ respectively). Baseline FSH levels were higher in non-obese subjects than in obese subjects ($p = 0.03$). There was no statistically difference between the two groups in LH-RH test responses. Eight (16%) of the obese and 13 (26%) of the non-obese subjects were diagnosed as CPP.

Conclusion: It was shown that height SDS and Δ BA-CA values were higher in obese subjects. Despite advanced bone age, rate of CPP diagnosis was low in the obese group. In obese girls, underlying biological mechanisms such as compensatory hyperinsulinemia, insulin resistance, endocrine disruptors, and androgens may be contributing to bone age progression and pubertal characteristic changes. Consequently those can be misleading for CPP predicting.

Keywords: Early puberty, Girl, Obesity, Advanced bone age

P3-269

IGSF1 mutation: treatment in the absence of symptoms?

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Introduction: Congenital central hypothyroidism is a rare pathology, whose molecular origin has been identified more frequently since discovery of the role of *IGSF1*. The natural evolution of central hypothyroidism in patients with mutations is not well known however.

Case report: A male infant born at term with a normal birth weight received thyroid function tests in the neonatal period because of symptoms of brain-lung-thyroid syndrome (generalized hypotonia, hyaline membrane disease). The tests in fact revealed

isolated central hypothyroidism (TSH, 3.8 mIU/L; T3, 1.56 pmol/L; T4, 6.2 pmol/L) with normal hypothalamic-pituitary MRI results. The patient had another episode of severe acute respiratory distress, and developed asthma. Endocrinological follow-up confirmed the isolated and persistent nature of TSH deficiency. NGS analysis revealed a c.2485dup variant of *IGSF1* (X-linked inheritance). Family investigations were performed. Tests revealed central hypothyroidism for both brothers. The elder brother (6 years old) has normal growth and psychomotor development and is completely asymptomatic. The younger brother (9 months of age) is asymptomatic but overweight. Thyroid tests were performed at day 3 of life for the younger brother because of family history. They revealed a low T3 level (3.5 pmol/l) and subnormal T4 level (11.4 pmol/l). No treatment was initiated. At 9 months of age, the T3 level had normalised (5.6 pmol/l) but the T4 level had decreased (8.2 pmol/l). At this stage, L-thyroxine treatment was initiated for both brothers, despite the absence of symptoms.

Discussion: This genetic variant has never been described in the literature but is considered pathological. The diagnosis, which would have eluded neonatal screening in France, was made because of the initial clinical presentation with respiratory distress, but these symptoms have not been reported for *IGSF1* mutations. The absence of symptoms in spite of clear central hypothyroidism has been described in the families of other index cases, and points towards the probable presence of compensating mechanisms, such as a possible increase in deiodinase levels, which would maintain a sufficient concentration of T3. This case highlights the variability of T3 and T4 levels in the absence of treatment in children, with a possible worsening of central hypothyroidism over time, suggesting that genetic testing in the family is essential to confirm diagnosis.

Conclusion: Prospective follow-up of this family should shed light on the natural history of central hypothyroidism and provide arguments for or against initiating treatment in the absence of symptoms.

P3-270

A real world, clinical experience of Burosumab therapy in a cohort of children with X-linked hypophosphataemia

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Burosumab, a monoclonal antibody targeting fibroblast growth factor 23, is now available for clinical use in children with X-linked hypophosphatemia (XLH). We explored the effects of this treatment in a clinical setting, considering biochemistry, growth, deformity, functionality, quality of life, pain and fatigue.

Methods: Clinical, biochemical, radiological and questionnaire data were reviewed at 6 and 12 months in a cohort of 8 children with XLH starting burosomab. Functionality was assessed with 6-minute walk test (6MWT) and Timed Up and GO (TUGLondon). Questionnaires included: Core Paediatric Quality of Life Inventory (PedsQL-Core), Paediatric Quality of Life multidimensional fatigue scale (PedsQL-Fatigue), and Brief Pain Index Pain Severity Score (PSS).

Results: Median age was 5.5 years (range=19 months-11 years). Table below shows radiological, biochemical and functional improvements over 12 months.

Test (Normal range)	Baseline Mean±SD	12 month Mean±SD	P value (Paired t-test)
Phosphate (1.0-1.9mmol/L)	0.7±0.1	1.1±0.1	P<0.001
ALP* (139-347IU/L)	415±73	322±70	P<0.001
PTH** (10-65ng/L)	31±14	42±16	P<0.05
Ur Ca:Creatinine (0.05-0.60)	0.44±0.21	0.37±0.23	Not significant, P=0.51
TmP/GFR ¹ *** (1.15-2.44)	0.56±0.11	1.19±0.18	P<0.001
Height Z-scores	-2.600±0.813	-2.435±0.787	P<0.05
Thatcher Scores (out of 10)	2.0±1.5	0.4±0.3	P<0.05
TUG (N=5,seconds)	5.7±0.5	4.8±0.6	P<0.05
6MWT (N=4,metres)	258±75	447±53****	P=0.05

*Alkaline Phosphatase, **Parathyroid hormone, ***Calculated ratio of renal tubular maximum phosphate reabsorption ****63-183metres below age/gender-matched norms

Deformity: Six children had lower limb deformity; varus(N=3), valgus(N=2), windswept(N=1). The most severely affected patient (intermalleolar distance=10cm) noted progression at 6 months with slight improvement by 12 months. All others noticed improvement at 12 months with reduced intercondylar/intermalleolar distances.

Pain/Fatigue: One child reported no pain. 12 month PSS decreased for 6 patients and slightly increased for one. Mean±SD PSS was 2.3±1.3 at baseline and 1.0±1.2 at 12 months (maximum score 10). Mean±SD PEDsQL-Fatigue scores were 64±19 at baseline and 76±17 at 12 months (maximum score 100,P=0.2).

Quality of Life: Mean±SD PEDsQL-Core score improved from 69±17 at baseline to 81±15 at 9 months, however decreased back to 67±17 by 12 months (N=7, maximum score 100). This is despite verbal reports of improvements and may reflect a shift in expectation.

Conclusion: In a real-world setting, burosumab can improve biochemistry, growth, deformity, pain and function in children with XLH.

P3-271

Psychosocial wellbeing of parents and quality of life of children (QoL) with 46, XY Disorders of Sex Development (DSD) attending the endocrine clinics at Lady Ridgeway Hospital (LRH) for children

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Introduction: 46, XY DSD leave lifelong implications on parents and patients. Documented scientific literature on children with 46, XY DSD is scarce in Sri Lanka. This study assesses the psychosocial wellbeing of parents and the quality of life in children with 46 XY DSD.

Objective: To assess the psychosocial wellbeing of parents and the quality of life in children with 46, XY DSD attending the endocrine clinics at Lady Ridgeway Hospital (LRH). Sri Lanka

Method: A descriptive cross-sectional study was done by interviewer administered questionnaires over one year from August 2017, among a cohort of 51 children with 46, XY DSD. QoL was assessed in a sub-group of 21 children aged 12 to 16 years. Psychosocial health-related QoL of children was assessed by the PaedQL-4.0 tool covering emotional, social and school functioning domains. Psychological morbidity and psycho-social wellbeing were assessed in both parents. For these, General-Health-Questionnaire-30 (GHQ-30) and a judgementally-validated questionnaire were used. Ethics approval was obtained from Sr Lanka College of Paediatricians and LRH.

Results: The median age of the cohort was 60 (6 to 147) months, majority (n=42, 82.4%) of whom had been reared as boys. 28 (53%) mothers and 23 (45%) fathers had psychological-morbidity when assessed with GHQ-30 with a cut-off score of 6. Patients' age was negatively correlated with GHQ-scores of both parents (p<0.05). The median psycho-social well-being scores were 44.0 (40.0-52.0) and 50.8 (44.0-56.0) for mothers and fathers which were positively correlated (p<0.001). The psycho-social well-being scores were negatively associated with age of the child (p<0.01). The median scores of PaedQL were 75 (60.8-78.3) and 73.3 (58.3-80.8) respectively for parental and child components. Scores of the parental-component of QoL was negatively associated with age of the child (p<0.01), but non-significantly with the education level of parents, family income and EMS score (p>0.05). Among school-aged children (> 5 years), 17 children (65.4%) were not drinking water in school, 15 (57.7%) did not use wash-rooms and 17(65.4%) did not participate in sports due to fear of exposure.

Conclusions: 46, XY DSDs are conditions associated with significant psycho-social morbidity in parents and psychological distress in the affected children in Sri Lanka.

P3-272**The effect of aromatase inhibitors on treating adolescent boys with short stature: A meta-analysis of randomized controlled trials**

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Objectives: Recently, aromatase inhibitors are increasingly prescribed as an alternative off-label therapy for short stature in boys, yet its efficiency is controversial. This study aimed to evaluate the effect of aromatase inhibitors on the treatment of short statured boys in adolescence by a comprehensive meta-analysis of published randomized controlled trials.

Methods: Literature search, quality assessment and data extraction were completed independently and in duplicate. Statistical analysis was completed using the STATA software. Effect-size estimates are expressed as weighted mean difference (WMD) with 95% confidence interval (CI).

Results: Seven randomized controlled trials including 265 short statured adolescent boys are eligible for analysis. Overall analysis showed that changes in predictive adult height were greater in the intervention arm than in the control arm (WMD: 3.42 cm; 95% CI: 0.76 to 6.09; *p*: 0.012), as well as in final height (WMD: 3.49 cm; 95% CI: 0.89 to 6.09; *p*: 0.009), final height standard deviation score (WMD: 0.46; 95% CI: 0.19 to 0.74; *p*: 0.001), height gain (WMD: 4.22 cm; 95% CI: 0.46 to 1.25; *p*: 0.005) and height standard deviation score for bone age (WMD: 0.86; 95% CI: 0.46 to 1.25; *p* <0.001). In contrast, bone age progression in the treatment arm was significantly slower than that in the control arm (WMD: -1.01 years; 95% CI: -1.71 to 0.74; *p*: 0.005). Meta-regression analysis indicated that treatment interval and trial quality were possible causes of heterogeneity (*p* <0.05). There was a low probability of publication bias as reflected by Egger's tests.

Conclusions: This meta-analysis provides evidence for the effectiveness of aromatase inhibitors in the treatment of adolescent boys struggling with short stature. Despite the optimism that aromatase inhibitors are effective in gaining an obvious height increase, clinical application of aromatase inhibitors in pediatrics is still largely pending reproducible clinical investigations on the challenge to tailor optimal pharmacologic dosage and treatment interval for the best possible outcomes for short statured boys in adolescence.

The main results are shown in the Table.

	IGHD			MPHD		
	Start	End	<i>p</i>	Start	End	<i>p</i>
Weight (kg)	15.6 ± 9.3	49.2 ± 16.6	<0.001	22.7 ± 9.4	38.9 ± 11.8	<0.001
SF (mm)	10.2 ± 6.1	15.2 ± 7.3	<0.001	11.7 ± 5.9	16.2 ± 7.5	0.001
HOMA	3.4 ± 3	1.6 ± 2.4	0.31	1.7 ± 1	1.3 ± 1.4	0.32

P3-273**Insulin sensitivity as HOMA at start and end of hGH treatment of children with congenital (c) IGHD and MPHD**

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Background: Patients with congenital IGHD or MPHD develop adiposity already "in utero". The effects of growth hormone (GH) treatment on adipose tissue are controversial, many claiming that GH reduces body fat (1,2). In addition there are reports that long-term GH treatment causes glucose intolerance, insulin resistance, followed in some instances by diabetes (3).

Objective: To determine whether long-term hGH treatment of children with cIGHD or cMPHD, using the low recommended dose, causes insulin resistance.

Subjects: Forty patients with cIGHD (22M, 18F) and 46 patients with cMPHD (28M, 18F) were included in the study. The mean age at start of hGH was 7 and 10yrs respectively. The mean duration of treatment was 8.5 yrs.

Methods: This is a retrospective study. Data on weight, BMI, subscapular skinfold thickness (SF), was collected from Medical Records of our clinic. HOMA was calculated using the formula HOMA-IR = Glucose x Insulin ÷ 22.5. The dose of hGH was 33µg/kg/d. Statistical analysis was by ANOVA.

Results: Parallel data on weight, BMI, subscapular skinfold thickness (SF) was found in 35 patients with cIGHD, and in 37 patients with cMPHD.

It is seen that in both groups the changes in weight and SF between initiation and end of treatment, were statistically significant denoting an increase of adipose in response to hGH.

HOMA was slightly elevate at the start of treatment in both groups and did not change significantly during treatment (norm:<2). The BMI measurements not contributory. Two patients developed diabetes between ages 39-50.

Conclusions: Despite a significant increase in adiposity, low dose long-term hGH treatment does not influence insulin sensitivity.

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P3-274

Role of adiposity indexes in the risk of ketoacidosis (DKA) in children with type 1 diabetes (T1D) at onset

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Background: DKA is the most serious life-threatening acute complication of T1D. Few data are available evaluating the possible role of anthropadiposity indexes in paediatric DKA in a selected population of prepubertal children. We aimed to identify the possible correlation between adiposity indexes and the presence and severity of DKA at T1D onset.

Methods: 195 prepubertal children (84Female/111Male) diagnosed between October 2010 and December 2018 were evaluated. Only children older than 2 years and without signs of pubertal development (thus younger than 11 years and 12 years for female and male, respectively) were included. Anthropometric measurements (height, height-SDS, weight, weight-SDS, BMI, BMI-SDS) were determined. Fasting blood samples were collected for glucose, venous pH, electrolytes, bicarbonate and glycosylated hemoglobin (HbA1c) measurement. The presence or absence of DKA was evaluated. According to pH values DKA severity was categorized as mild, moderate, and severe. A Spearman test was performed to evaluate any possible correlation between BMI-SDS values and the main variable of interest at onset. In order to characterize the effects of adiposity on the main variables of interest at onset, the study population was divided according to BMI-SDS into three tertile groups. The Kruskal-Wallis analysis was performed to evaluate differences across the tertile groups while the Mann-Whitney test for the post hoc analysis.

Results: DKA at onset was reported in 36% of subjects (N=71/195). No difference in term of severity of DKA was documented between gender. We demonstrated a significant association between venous pH and BMI-SDS of children at the time of T1D diagnosis. HbA1c and age of onset for diabetes were inversely related to BMI-SDS. Glycaemia, HbA1c and pH values were significantly different across the three tertile groups. Glycaemia and HbA1c were significantly higher while the pH values significantly lower in first tertile of BMI-SDS than the third tertile. A progressive reduction in prevalence of DKA and its degree of severity was highlighted, with the increasing of the BMI-SDS tertiles. Children with lower BMI-SDS at the onset had an increased risk of severe DKA compared with those with a higher BMI-SDS.

Conclusions: Adiposity indexes correlate significantly and directly with the presence and degree of DKA at the onset of T1D in children. BMI-SDS values are directly correlated with pH values and inversely with HbA1c levels and an age of onset of DKA. With the increase of the BMI-SDS tertile, we observe a progressive reduction in the prevalence of DKA and its degree of severity.

P3-275

Serum spexin is correlated with lipoprotein(a) and androgens in normal-weight, overweight and obese adolescent females

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Background: The Spexin gene is considered the most dysregulated in obese human fat with an almost complete absence of expression in obese human fat in comparison with non-obese fat tissues. Limited data from human and animal studies suggest that the novel peptide spexin may potentially impact food intake, weight regulation and body adiposity.

Objective: The aim of this study was to compare serum spexin concentrations between normal-weight and overweight/obese adolescent females and explore possible relationships between circulating spexin and anthropometric, hormonal, metabolic, bone and body composition parameters.

Methods: Study participants included adolescent females, aged 12-18 years, who presented to the Centre for Adolescent Medicine and UNESCO Chair on Adolescent Health Care, from May 2016 to June 2018. Exclusion criteria included severe comorbidity, chronic medication, contraceptive use and pregnancy. Adolescents underwent evaluation of their anthropometric, metabolic and hormonal parameters as well as assessment of their bone mineral density and body composition with the use of dual-energy x-ray absorptiometry. Serum spexin concentrations were measured by ELISA using the Spexin (Human) EIA Kit of Phoenix Pharmaceuticals (USA) with analytical sensitivity of 0.08 ng/ml. Comparisons of continuous data were carried out with the use of student *t*-test or Mann-Whitney U test for non-parametric data. Pearson or Spearman's rho correlation coefficients identified correlations between continuous variables. The International Obesity Task Force cut-offs for body mass index (BMI) were used to categorize adolescents into normal-weight, overweight and obese.

Results: A total of 80 adolescent girls aged (mean±SD) 16.23±2.26 years; 55 normal-weight females (mean age±SD,

16.69±2.22 years; mean BMI±SD, 19.72±2.52 kg/m²), 25 obese and overweight females (mean age±SD, 15.17±2.01 years; mean BMI±SD, 29.35±3.89 kg/m²), participated in the study ($p=0.005$ and $p<0.001$ respectively). No significant differences ($p=0.378$) were observed in serum spexin concentrations between normal-weight and obese/overweight adolescents.

Circulating spexin levels were not correlated with BMI or body fat percentage. In the total sample, serum spexin concentrations were correlated with Lp(a) ($rs = 0.402$, $p = 0.046$). In the obese/overweight adolescents serum spexin concentrations were correlated with total testosterone ($rs = 0.727$, $p = 0.011$) and free androgen index ($rs = 0.755$, $p = 0.007$), whereas in the normal-weight participants spexin levels were correlated with dehydroepiandrosterone sulphate (DHEA-S) ($rs = -0.445$, $p = 0.038$).

Conclusion: The proposed role of spexin in adolescent females needs to be further investigated in large study samples.

P3-276

Exocrine pancreatic insufficiency and vitamin K deficiency associated to Octreotide therapy in congenital hyperinsulinism: An under-recognized potential adverse effect

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Abstract: Congenital hyperinsulinism (CH) is the most frequent cause of persistent hypoglycemia in the newborn. Octreotide, a long-acting somatostatin analogue (SSA), is a second line treatment for diazoxide unresponsive CH patients. Although it has been found to be a safe and effective treatment, long-term benefits and side effects have not been thoroughly evaluated. Furthermore, some authors have emphasized that exocrine pancreatic insufficiency is a common but under-recognized adverse reaction in adults treated with octreotide. To our knowledge, no pediatric patient with somatostatin analogue-induced pancreatic exocrine insufficiency has been reported to date.

Objective: Our aim is to report the first case of an infant with CH and exocrine pancreatic insufficiency and secondary vitamin K deficiency, associated to Octreotide therapy.

Case report: A 7 month and 3 week old male with diazoxide unresponsive diffuse CH (heterozygous autosomal dominantly mutation in the ABCC8 gene; NM_000352.4:c.357del) was found with bruising of legs, back and forearms after two months of SSA

treatment onset (8.9 µg/kg/day divided into 4 daily doses). In addition to intermittent capillary blood glucose measurement, Real-time subcutaneous continuous glucose monitoring was used for glycemic control (Guardian™ Sensor 3; Medtronic Diabetes, Northridge, CA, USA). Bruises and bleeding remnants were also observed at the puncture points of the sensor. Laboratory findings identified vitamin K deficiency as the cause of the cutaneous hemorrhagic syndrome with an abnormal coagulation values [prothrombin time 117.4 seconds - Reference range (RR) 11.5-15.3 seconds-; International Normalized Ratio 9.1 - RR 0.8-1.2 -; Activated Partial Thromboplastin Time 88.4 seconds - RR 35.0-46.0 seconds-; serum fibrinogen 340 mg/dl - RR 150-380 mg/dl-] and a decrease in all vitamin K-dependent proteins (Factor II: 4% -RR 70-120 %; Factor VII: 10 % -RR 55-170 %; Factor IX: 8 % -RR 60-150% and Factor X: 3% -RR 70-120 %). Coagulopathy was resolved with vitamin K treatment (5 mg/day intravenous; 3 days). The patient was discharged without incidents. Further investigations revealed association of steatorrhea, (fat fecal quantification: 18.8 -19 g fat/day -RR < 6 g/d-) and stool fecal elastase-1: 120 mcg/g -RR > 200 mcg/g-), both markers of malabsorption. Other causes (cystic fibrosis and bacterial overgrowth syndrome) were excluded.

Conclusion: We report the first pediatric case of exocrine pancreatic insufficiency and vitamin K deficiency associated to Octreotide therapy in congenital hyperinsulinism, emphasizing the potential adverse effects and clinical relevance of the exocrine pancreatic insufficiency associated to Octreotide treatment.

P3-277

The Role of Urine AVP in the Diagnostic Pathway of Polyuria and Polydipsia Syndrome

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Background: Polyuria and polydipsia syndrome (PPS) workup is not straightforward, especially in children. Basal investigations are often not reliable in distinguishing among diabetes insipidus (DI), central (CDI) or nephrogenic (NDI), and primary polydipsia (PP). Water deprivation test (WDT) is often essential, although uncomfortable and not always reliable enough to recognize partial DI. Plasma AVP investigation is not routinely used in the diagnostic pathway as AVP measurement is technically difficult for the hormone instability and the high in vitro thermolability. Urine AVP (U-AVP) assessment, on the contrary, is not biased by the same complications and was firstly proposed in early 2000s, but not further developed later on. We investigated U-AVP in a small group of patients with PPS and in a control group.

Methods: We retrospectively assessed AVP in urine samples of patients presenting with PPS (2M,3F), after more common causes of polyuria were excluded. Urine samples were collected

as basal and during WDT, along with plasma and urine osmolality (PO–UO). Patients were diagnosed with CDI (1M,1F) and PP (1M,2F) on the basis of PO and UO values during WDT, according to standard reference ranges. DDAVP test was performed to discriminate NDI from CDI. Furthermore, we collected blood and urine samples for PO, UO and U-AVP in a control group (5M,8F), who had no history of PPS and with normal neuropituitary bright spot at MRI. SPSS program was used for statistical analysis. Commercial RIA kit was used for U-AVP analysis.

Results: U-AVP was measurable in all urine samples collected in control and PP group. Mean U-AVP was significant higher in controls than PP patients, 59.9 and 15.3 pmol/l respectively ($p<0.5$). U-AVP was directly correlated to urine osmolality both in control and PP group ($p<0.01$, $R^2=0.32$). U-AVP was undetectable on basal urine samples of CDI patients. U-AVP increased during WDT in PP patients. Conversely, CDI patients did not show significant U-AVP increase to prevent PO over 300 mmOsm/kg. U-AVP increased in CDI patients during DDAVP-test.

Conclusions: We demonstrate that AVP can be directly, easily and painless assessed in urine. U-AVP seems helpful in distinguishing CDI from PP, and makes DDAVP test needless. U-AVP may play also a role in the assessment of adherence to treatment in CDI patients. Undoubtedly, larger cohorts are needed to validate the few data presented. Anyway, U-AVP analysis might be a new tool in the diagnostic pathway of the PPS and to co-adjuvate clinical decisions.

P3-278

New mutation of GNAS in a 2 year old oncological patient

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Introduction: Leydig cell tumors are rare (3% of testicular neoplasms). 80% of cases occurs in adult population, although a quarter is described in prepubertal patients older than four years. The clinic differs according to the patient's age. Activating mutations, acquired and limited to the tumor tissue, are described in exon 11 of the LH receptor gene. And in mixed Sertoli-Leydig tumors activating mutations of the Gs-alpha subunit of the stimulating G protein (GNAS) and in the DICER1 gene are described.

Case Description: We show a 2-year-old boy with testicular asymmetry, increase in penis size and thickness, and increase in weight, height, and growth rate. On examination, he showed hyperpigmented coffee-milk macules with a metameric distribution on the back and right upper limb, right testicle 10 cc and left testicle 3cc, and penis 8 cm long and 7.5 cm thick. On complementary tests he showed testosterone 4.02 ng/ml, antimulleriana hormone 22.96 ng/ml (both high), and AFP and stimulus test after GnRH negative. We observed, through ultrasound, heterogeneous lesion in the right testis compatible with Leydig cell neoplasia, which is confirmed in an anatomopathological study after tumorectomy with preservation of the testicle. In the tumor piece, a change of uncertain clinical significance c.180_185del (p.Met60_Arg61del) was detected in the GNAS gene. He received treatment with aromatase inhibitors and antiandrogens. After tumorectomy, testosterone were normal. Nowadays, close follow-up is maintained.

Conclusions: We show a Leydig tumor at an uncommon age, with a mutation in the tumor tissue not described in the GNAS gene in a non-mixed tumor. In childhood, the behavior is generally benign, especially in those with normal AFP levels at diagnosis. In these cases it is recommended conservative treatment, which decreases the risk of hypogonadism and subfertility. It is important close and prolonged follow-up, both because of the risk of recurrence, and the risk of central precocious puberty with changes on final size.

P3-279

Relation between levels of atymullerian hormone and inhibin B and spontaneous puberty in patients with Turner syndrome – preliminary results

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Introduction: Primary hypogonadism is stated as one of major features in patients with Turner Syndrome (TS), however it is not a constant finding. Variable markers of ovaries failure in TS patients are still missing. The present study aimed to evaluate the usefulness of atymullerian hormone and inhibin B assessment in predicting spontaneous puberty in patients with TS.

Methods: The study included 35 TS patients. Gonadal axis function (LH, FSH and estradiol levels) was evaluated at the age of physiological puberty (10-12 y.o), before introduction of hormonal replacement therapy. Additionally AMH and inhibin B levels were assessed. In follow up patients were divided into 2 groups: with spontaneous puberty (SP) and without (WP).

Results: Spontaneous puberty occurred in 16 patients at the mean age of 10 years (9-12 years). There were significant differences in levels of FSH (24.5 vs. 66.5, $p=0.002$), estradiol (28.4 vs 14.9, $p=0.005$), AMH (0.8 vs. 0.003 ng/mL, $p=0.001$) and inhibin B (29.1 vs. 1.06, $p=0.026$) in SP and WP patients. In three SP patients without elevated FSH level (FSH<35mIU/ml) AMH and inhibin B concentrations were zero. SP patients had mosaic (non 45, X) karyotype in 87,5 % (14/16) and monosomy (45, X) only in 12,5% (2/16). WP patients had mosaic (non 45, X) karyotype in 47 % (9/19) and monosomy in 53% (10/19).

Conclusion: AMH and Inhibin B levels seem to be a good marker of ovarian function in TS patient, especially in cases with discrepancy between clinical course of puberty and results of FSH and estradiol levels. Patients with non 45,X karyotype are more likely to develop spontaneous puberty.

P3-280**Short, but daily and controlled physical activity of children with obesity has a positive effect on the irisin and chemerin levels**

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Therapeutic interventions in obesity in addition to the weight loss, seek to improve the profile of cytokines. It is believed that physical activity, even in the absence of significant weight loss, may favorably increase the concentration of irisin and decrease the concentration of chemerin.

The aim of the study: Was to compare the impact of a standard lifestyle intervention (SI) with an intense intervention (II) including controlled increase of daily physical activity (from 5 up to 15 min. daily) on the concentration of irisin and chemerin in prepubertal children with obesity.

Material and Methods: 20 children (6 boys, 14 girls) at the mean age 8.9 (SD 1.4), randomly assigned to two groups, group 1 (starting with II), and 2 (starting with SI), after 3 months the groups have been switched.

Results: The reduction of BMI-SDS and fat% in the whole body was observed after both types of intervention [Δ BMI-SDS (-) 0.5 vs. (-) 0.2; Δ fat% (-) 2.9 vs. (-) 1.4] after II and SI respectively; the difference in mean change value not statistically significant for any parameter). After II mean irisin level increased from 4.8 μ g/mL to 5.1 μ g/mL in the whole group. The increase was even more significant in group 1 (4.7 μ g/mL vs. 5.4 μ g/mL), contrary to group 2, where no increase was noticed after II (4.9 μ g/mL vs. 4.7 μ g/mL). Mean chemerin level after II decreased from 66.4 ng/mL to 60.1 ng/mL in whole group. The more favourable change of mean chemerin level was noticed in group 1 (64.4 ng/mL to 58 ng/mL) than in group 2 (67.6 ng/mL to 66 ng/mL). The differences in mean change values were statistically significant ($p<0.05$) for both investigated cytokines.

Conclusion: Even short, but regular and controlled physical activity has a beneficial effect on the concentrations of irisin and chemerin in children with obesity.

P3-281**New Autosomal Dominant Mutation in Glucokinase Gene Causing Congenital Hyperinsulinism Diagnosed in Adulthood**

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Introduction: Autosomal dominant congenital hyperinsulinism (CH) is characterized by congenital hypoglycemia due to mutations in any of several genes including the glucokinase (GCK) gene. It is a rare disease with variable clinical symptoms mostly treated medically but in some cases requiring surgical intervention.

Aim: We describe herein the clinical presentation and the genetic diagnosis of CH in two generations of an Israeli family.

Methods/patients: The proband was a 25 years old male who presented with hypoglycemia (glucose 40 mg/dl normal range 70-100). He felt hypoglycemic symptoms from early age but was never treated medically. He served in the army as a combat soldier at the field unit. His mother and his brother were found to be hypoglycemic but were never treated medically. His other brother was normoglycemic.

Results: DNA sequencing of GCK gene identified a novel heterozygous missense mutation (p.(Lys459Asn), c.1377G>C) in exon 10 in the proband, his mother but not in his normoglycemic brother. Continuous glucose monitoring revealed asymptomatic low glucose levels down to 40 mg/dl (normal range 70-100) during day and night.

Conclusion: CH characterized by hypoglycemia due to a mutation in the GCK gene was diagnosed in two generations of an Israeli family. The congenital condition was not treated by medications. The mutation does not cause an unregulated insulin secretion, but highly regulated insulin secretion with a below normal basal glucose level. It is the mirror picture of the CGK mutations causing MODY 2 (maturity onset diabetes of the young). Therefore the patients do not reach life endangering situations and may be not treated medically. Obtaining a detailed personal and family medical history and, when appropriate, performing targeted genetic testing, is critical to correctly diagnose hyperinsulinemic hypoglycemia. Identifying the genetic etiology has important implications regarding medical therapy and follow-up.

P3-282

Abstract withdrawn

P3-283**Comparison of Densitometric Aspects During the Transition Period in Patients with Congenital and Acquired Pituitary Deficiency: First Argentine Experience**

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The transition phase is the period from the end of puberty until achievement of full adult maturity. We report the results from 45 patients with pituitary deficiency (15-24.9 years), 28 (16 males) with congenital insufficiency (G1) and 17 (10 males) with acquired disease (G2), evaluated at the end of GH therapy. All cases had confirmed GH deficiency; 89.2 % of cases from G1 had multiple pituitary deficiencies (TSH 23/28, LH/FSH 19/28, ACTH 15/28 and Prolactin 3/28), 94.1 % of cases from G2 had multiple deficiencies (TSH 16/17, LH/FSH 15/17, ACTH 13/17 and Prolactin 1/17); adequate replacement was confirmed in all cases. Patients with congenital disease received GH therapy (Median and range) from 7.75 years old (0.5-16.1) for 8.25 years (2.9-19.5) and those with acquired deficiency, from 12.85 years old (4-18) for 4.75 years (1.9-12.4). Heights achieved (cm) were: 148 (138.5-167.3) and 164.3 (152.2-176.5) in females and males from G1, respectively and 158 (143-164) and 168.25 (154.2-176), respectively from G2. We assessed body composition and bone mineral density (BMD) of the left femoral neck (FN) and lumbar spine L1-L4 (LS) by densitometry (DEXA, LUNAR equipment).

As 11/28 patients from G1 and 4/17 from G2 had near final height under the 3rd percentile, a sub-analysis of BMD was performed in patients with normal height and no significant differences were found in FN and LS. No differences were found in the number of patients with spontaneous or induced puberty in both groups.

Conclusions: The lower BMD of G1 might be related to different factors including, but not limited to, duration of the deficiency, severity (lower IGF-1 values) and/or lower final height. It is interesting to highlight that differences in BMD did not persist when excluding patients with low height. It is known that areal BMD may be underestimated in subjects with a small skeleton; therefore, in these cases, volumetric BMD measurement should be ideally performed. Our findings would suggest the need for GH therapy optimization during childhood, not only to improve final height, but also to achieve better bone quality.

Md and Range	IGF1(SDS)	Lean mass(%)	Fat mass(%)	FN(z score)	LS(z score)
G1	-3.7* (-10 to -1.9)	60.1** (48.8 to 71.2)	35.6** (24.6 to 51.1)	-1.15*** (-3.9 to 0.7)	-1.8**** (-5.0 to 1.3)
G2	-3.5 (-16 to 1.4)	59.9 (44.5 to 71.9)	38.8 (20.5 to 52.6)	-1.1 (-1.6 to 0.9)	-1.57 (-2.4 to 0.8)
p vs G2	*0.019	**NS	**NS	***0.06	****0.0039

P3-284**Demographic, clinical and biochemical characteristics of pediatric obesity: interim analysis of a larger prospective study**

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Background: Pediatric obesity is the most common nutritional disorder that affects more than a third of the young population and predisposed individuals to greater future morbidity and mortality. Therefore, rising obesity epidemics becomes is becoming one the most important healthcare problems.

Methods: In the period of 2017-2018, 62 consecutive pediatric patients referred to the University Pediatric clinic were recruited. Demographic and clinical information for both the patients and their parents were collected using in-person interview and standarized questionnaires. Specific data regarding weight, height, systolic (SP) and diastolic (DP) blood pressure, lipid metabolic profile, thyroid and adrenal hormone levels, and glucose and insulin levels before and after oral glucose tolerance test (OGTT with 75g glucose dose) were collected. Body mass index was determined and patients were classified based on the International Obesity Task Form (IOTF) criteria. Appropriate descriptive, comparative parametric and non-parametric tests and Spearman's ranked correlations were used for statistical analysis.

Results: The population was consisted of 34 males and 27 females with respective age of 11.3 and 11.7 years old ($p=0.781$) were recruited. The mean BMI was 30.5 (SD 5.5), of which 8 were with normal weight (≤ 25 BMI), 22 were overweight (25-30 BMI) and 32 were obese (≥ 30 BMI). Patients BMI was significantly associated with the BMI of their parents (Spearman's ranked $r=0.293$, $p=0.033$). Both SP and DP were significantly different between the BMI subgroups (one-way ANOVA $p=0.005$ and $p=0.001$, respectably) with the obese group having the highest BP values (post-hoc Benjamini $p=0.004$). The obese group had a trend of

lower T4 when compared to overweight and normal pediatric patients (7.0mg/dL vs. 9.4mg/dL vs. 10.4mg/dL, one-way ANOVA p=0.061). The obese group had lowest baseline glucose (4.0mmol/L vs. 4.9mmol/L vs. 4.5mmol/L, one-way ANOVA p<0.001) but largest numerical increase during the OGTT (D3.5mmol/L vs. D2.6mmol/L vs. D2.0mmol/L, one-way ANOVA p=0.137). Along those lines, the obese group had the greatest levels of insulin at rest (21.8mgU/mL vs. 12.9mgU/mL vs. 13.6mgU/mL, one-way ANOVA p=0.008). Furthermore, the obese group had numerically the smallest insulin response after oral glucose tolerance test (D86.1mgU/mL vs. D125.7mgU/mL, p=0.08).

Conclusion: Pediatric patients in our clinic demonstrate familial type of obesity which is characterized with premorbid asymptomatic endocrine impairments. In order to maintain normal glucose levels, obese pediatric patients demonstrate high levels of resting insulin levels and diminished response after OGTT load. Failure of these compensatory mechanisms may lead to early development of diabetes type 2.

P3-285

Mental health of both child and parents play a larger role in health related quality of life of obese and overweight children

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Aims: A decrease in health-related quality of life (HRQOL) measures among obese and overweight (OB/OW) children has been shown in several studies, but very little is known about the variables affecting HRQOL impairments. The aim of this study was to evaluate the relationship between HRQOL and sociodemographic characteristics, anthropometric measurements, metabolic parameters, mental symptoms and parental attitudes in the sample of OB/OW children.

Method: Eighty-six OB/OW children, aged between 9–17 years, were participated. We performed sociodemographic questioning, physical examinations including anthropometry and laboratory evaluations of the participants. HRQOL was assessed using the Pediatric Quality-of-Life Inventory (PedsQL), levels of anxiety and depressive symptoms using The Children's Depression Inventory (CDI) and Screen for Child Anxiety Related Disorders (SCARED) questionnaire respectively and parental attitudes through use of the Parental Attitude Research Instrument (PARI) questionnaire.

Results: A significant relationship was found between total scores of CDI and SCARED answered by children and the total and subscale scores of PedsQ. Scores of total quality of life subscale, physical functionality and emotional functionality subscales were significantly lower in children with family history of mental illness. No significant relationship between PedsQL subscales and anthropometric and metabolic parameters was found.

Conclusions: Therefore, emotional problems and parental psychological distress are important factors that need be considered in models of HRQOL in this population.

Key words: Obese Children, Parents, Quality of life, Mental Health

P3-286

Alterations in ambulatory blood pressure in adolescents with obesity

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Introduction: Obesity is associated with comorbidities such as hypertension (HTN), and other alterations in blood pressure (BP) such as: masked hypertension and alterations in the circadian cycle variability, that only can be detect through ambulatory blood pressure monitoring (ABPM).

A higher prevalence of masked hypertension has been reported in obese subjects, up to 4.3%. Also a loss in drop from mean daytime to mean night-time levels in up to 50%, conditions that only can be detected by ABPM.

Subjects and methods: This was a cross-sectional study of adolescents aged 12–17.9 years recruited at their first visit to any of two participating Childhood Obesity Clinics in Mexico City. We carried a medical and nutritional evaluation, anthropometry, biochemistry analysis (fasting glucose, lipid profile, insulin and renal function) and measurement of casual BP by osillometric. After that, the monitor was placed in the subjects for 24 hours ABPM records.

Results: Thirty subjects were measured, of which 66% are women, with BMI values between 26.5 and 35.14 kg/m²; with a median age of 15 years.

The biochemical results were reported as median, glomerular filtration rate 101.31ml/min 1.73, glucose 83mg/dl, total cholesterol 145mg/dl, triglycerides 107mg/dl, and uric acid 6.1mg / dl. 37% had hypertriglyceridemia, 7% hypercholesterolemia and 97% had central obesity.

The frequency of ABPM alterations were: 22% of men and 21% of women had systolic HTN of 24hrs; 11% of men and 26% of women had diastolic HTN of 24hrs; 22% of men and 21% of women with systolic-day HTN, 11% of men and 16% of women with diastolic-day HTN; while for systolic-nocturnal HTN, 33% of men and 32% of women presented it. Diastolic-night HTN in men was 44% and 53% in women. The most frequent alteration was nocturnal diastolic HTN.

The no dipping in BP was present in 50% of the subjects, with systolic predominance; the diastolic was in 33% of the subjects.

The main alterations of the TA were documented during the night. One patient presented the seven alterations of ABPM. Loads greater than 50% were observed in 13 patients (43%) that imply severe ambulatory HTN.

Conclusions: 70% of adolescents with obesity presented some alteration in ABPM, with a predominance of nocturnal HTN and the absence of dipping.

It is important to consider measure ABPM as part of the assessment of adolescents with obesity, as well as to evaluate the comorbidities related to this alteration, such as hypertrophy of the left ventricle.

P3-287

Should we review clinical criteria to diagnose SHOX gene mutations?

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The mutation of the SHOX gene is a cause of short stature by varying frequency depending on the published work, but estimated at around 3-10 % of cases of short stature. The main diagnostic scheme for starting genetic testing is the Rappold score, which requires clinical and radiological criteria, under which this form of short stature is framed as a disharmonious. In our clinical experience, however, we also looked for mutations in the SHOX gene in patients with signs of growth hormone deficiency as defined by the Italian legislature with the note of the Italian drug agency AIFA, such as a defiance of stature growth speed, significant short stature or insufficient pubertal growth spurt. In the last ten years, we have assessed 496 boys and girls with the above criteria. We diagnosed GH deficiency in 50 cases and mutations in the SHOX gene in 10 cases, two of which achieved the minimum score predicted by the Rappold scheme. There was always at least one parent with short stature. Growth hormone was given at the dose of 0.035-0.05 mg/kg/die until the final stature (two cases) was reached, always with

good stature response and with a final height within the genetic target (see table). In our opinion, we need to review the criteria for accessing genetic diagnostics for SHOX mutations, performing this survey in all cases that require investigations for suspected GH deficiency.

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P3-288

Circulating chemerin may be associated with early vascular pathology in obese children without overt arterial hypertension – preliminary results

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Elevated chemerin level is observed in obese patients with metabolic syndrome and arterial hypertension but it is not known if measurement of this hormone have any prognostic value before the occurrence of clinically overt complications of obesity. The aim of the study was to investigate the relationship between serum chemerin level and 24h blood pressure monitoring (ABPM), and intima media thickness in obese children.

Methods: The study included 23 children (13 girls, mean age 9.3, SD 1.9) with obesity (mean BMI SDS 3.9, SD 1.7) without overt

Pt	Sex	Age of diagnosis	Rappold score	H SDS at diagnosis	Bone Age at diagnosis	Target height cm	H SDS at last visit	Final height cm	Gene anomaly
1	M	2.04	2	-2,9	1.5	169.6	-2		microdupl
2	M	14.9	2	-2,4	13	170,5	-2		microdupl
3	M	12.35	0	-1,7	10.5	173.2	-1,2		microdupl
4	F	5.7	2	-1,4	4.5	157.6	-0,7		ENHANCER
5	F	3.5	0	-0,8	2.5	159.5	-0,6		del
6	M	7.7	0	-1,5	5.5	169.8	-1,1		del
7	M	12.6	2	-1,7	11	175	-0,2	174.6	microdupl
8	F	12,8	4	-2,7	13	149,4	-2,6	147.9	del
9	M	8.7	4	-1	7.5	161.4	-0.9		del
10	M	10.4	6	-1,7	7,5	154	-1,2		del

arterial hypertension, and metabolic complications of obesity. ABPM, ultrasound of carotid arteries and aorta, and plasma chemerin concentrations quantified by ELISA, were performed in each participant.

Results: There was no significant correlation of circulating chemerin with anthropometric measurements (BMI SDS, weight to height excess, waist circumference, fat percent in the whole body). There was a significant correlation of circulating chemerin level with systolic blood pressure load in ABPM ($r=0.5$, $p<0.05$). There was no significant correlation of circulating chemerin with ultrasound markers of atherosclerosis (carotid intima media thickness $r=0.4$, aorta intima media thickness $r=0.3$).

Conclusion: Increased concentration of chemerin is an important risk factor for increased systolic blood pressure in children with obesity, even before clinically overt hypertension develops.

P3-289

Quality of Life of patients with Type 1 Diabetes

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The objective of the study was to evaluate the Pediatric Quality of Life (PedsQL) of children from 8-12 y/o with T1DM, to compare PedsQL perceived by their parents, to understand gender and other factors influence on PedsQL and disease management.

We conducted a prospective non-randomized cross-sectional study. Children with T1DM were identified from pediatric endocrinology department registries. The onset of diabetes had to be more than 6 months. All consecutive patients from Armenia aged 8-12 years old with type 1 diabetes were included in the study. For the study, we used the validated adapted PedsQL Inventory 3.0 Diabetes Module of the child. Clinical variables analyzed were: time since diagnoses (in years), BMI, HbA1c, diet and exercising habits, frequency of hypoglycemia, comorbidity, insulin injected by child or parent.

Results: A total of 132 children aged 8-12 years with T1DM and their primary caregivers ($n = 132$, 100% mothers) participated in this study including 60 (45.45%) girls ($6.6 (\pm 2.75)$ y/o) and 72 (54.55%) boys ($7 (\pm 1.54)$ y/o) ($p=0.318$). Parents were either uneducated 84 (63.64%) or had a secondary school education 48 (36.36%). The reported frequency of hypoglycemia occurred in 72 (54.55%) children. In most of the cases, insulin was injected by child 84 (63.64%). The mean age of T1DM years was $6.82 (\pm 2.17)$. HbA1C mean level was $8.42 (\pm 1.5)$. We found that HbA1c control can be influenced by parent/guardian and child through appropriate disease management which in turn can increase QOL. We identified lower scores of QOL reported by child versus primary caregivers. In group children girls seem to be more sensitive towards pain and difficulties associated with the disease, boys experience more difficulties related to treatment compliance and parents' involvement. Parents' education plays a significant role in the management of a child's disease and QOL.

P3-290

Etiologies and clinical patterns of Hypopituitarism in Sudanese children

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Background: There is paucity of information regarding etiology and clinical profile of hypopituitarism from populations with high rates of consanguineous marriage like Sudan. We report the first data on etiological factors and clinical profiles of children with hypopituitarism from Sudan. **Methodology:** This study was a descriptive, hospital based, retrospective study carried out in two major pediatric endocrinology centers in Sudan (Khartoum state) from January 2006 up to December 2014. Patients' records were reviewed (both in and out patient). Relevant demographical, clinical, hormonal and image data were collected using data collection sheets.

Results: The study included 156 patients. One hundred and one patients were males (M: F 1.8:1). The commonest age groups were those more than 10 years (adolescents) and represented 57.7 % of patients. Consanguinity was seen in 77.8 % of patients overall and in 91% of patients with congenital etiologies. The commonest clinical presentations were short stature and poor growth (93.5%) and delayed puberty (35.3%). Congenital causes (86.5%) were more prevalent than acquired causes (13.5%) there were six family clusters with multiple pituitary hormone deficiency and three families with isolated growth hormone deficiency. Most of the congenital cases of multiple pituitary hormone deficiency (MPHD) were phenotypic for Prop1 mutation (77.5% of sporadic cases and 50% of inherited cases). Craniopharyngioma was the commonest acquired cause, seen in 16 (10.2%) patients. Growth hormone was the most frequent hormone deficient (89.7%), The number of patients with congenital isolated growth hormone deficiency (IGHD) were higher (46.1%) than those with congenital MPHD (37.1%). MRI brain findings were significantly abnormal in patients with congenital MPHD more than those with congenital IGHD.

Conclusion: Hypopituitarism in populations with high rates of consanguineous marriage maybe at a higher incidence than international data. Growth hormone deficiency is the commonest hormone deficiency found either isolated or as part of multiple hormone deficiency. MRI brain imaging is of high value in the diagnosis of hypopituitarism. Genetic studying is of great value in populations with high rates of consanguineous marriage such as Sudan.

Rare causes for paediatric virilizing tumors

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Introduction: Excessive androgen secretion from gonads, adrenal gland and tumors arising from germ cells lead to gonadotropin independent precocious puberty in male and virilization in females. Rapid progression of symptoms with peripheral precocity need urgent evaluation to identify the underlying etiology. We report three cases of malignancy with excess androgen secretion within a year in a tertiary care children hospital in Sri Lanka.

Case Series

Case 1: 4 year old boy presented with iso-sexual precocious puberty, cushingoid feature and abdominal distension for six months duration. Examinations revealed a left side abdominal mass. Imaging showed L/adrenal mass without metastatic spread. He had high dihydro epi andro steridione (DHEA) and testosterone. He underwent tumour resection. Histology revealed adrenocortical carcinoma (ACC). He is been followed up with three monthly DHEA and USS abdomen to look for tumour recurrence. ACC is a rare but very dangerous cancer of the adrenal gland. It is found in 1 in million people and is common before 10 years in children.

Case 2: 13 year old girl presented with virilization. She had elevated alpha feto protein and testosterone. Imaging revealed soft tissue mass arising from right ovary without distance metastasis. She underwent right side salpingo oophorectomy with left side ovarian biopsy. Histology revealed, bilateral sertoli ladyig cell tumor (SLCT). She was referred to oncologist for chemotherapy and subsequently planned for left side salpingo oophorectomy. SLCT is a rare sex cord-stromal tumor. Prevalence is less than 0.5% of all primary ovarian neoplasms. 75% reported cases are in the second and third decades of life. SLCT affecting bilateral ovaries are extremely rare and account for only 1.5–2.0% of all the cases.

Case 3: 8 year old boy presented with peripheral precocious puberty. He had high testosterone and elevated β HCG. Ultra sound showed testicular microlithiasis. His brain and abdominal imaging with CT and MRI were normal. Even though the chest x-ray didn't have mediastinal widening, CT thorax showed an anterior mediastinal mass. He underwent video assisted thoracoscopic biopsy. Surgical resection was carried out as the frozen sections were inconclusive. Histology revealed seminoma without other evidence of germ cell components. He received cisplatin based chemotherapy for his seminoma. Extra gonadal germ cell tumors (EGGCTs) are rare with the incidence of 1 in 1,000,000.

Conclusion: High degree of clinical suspicious along with biochemical and radiological investigations help to diagnose very rare virilizing tumors.

GnRHa Are Effective to Treat Short Stature Children with Normal Puberty: A Systematic Review and Meta-Analysis

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Objective: Short stature is a common pediatric problem, and it has aroused a wide public concern. There are a number of effective treatments available for short stature, but which one is better remains largely controversial. We aimed to test the hypothesis that gonadotrophin-releasing hormone agonists (GnRHa) can increase final height in short stature children with normal puberty via a meta-analysis on comparative controlled trials.

Methods: Literature search was conducted before March 25, 2019. Data extraction and quality assessment were two authors independently completed in duplicate. Effect-size estimates are expressed as weighted mean difference (WMD) and 95% confidence interval (95% CI).

Results: Five randomized controlled trials and 4 non-randomized controlled trials involving total 340 short stature children with normal puberty were eligible for analysis. Overall, GnRHa treatment resulted in significant gains in height standard deviation score (SDS) (WMD: 0.60 and 0.77 relative to initial height SDS and predicted height SDS; 95% CI: 0.26 to 0.94 and 0.27 to 1.27; $p = 0.001$ and 0.003, respectively) and height (WMD: 4.52 cm and 6.0 cm relative to initial height and predicted adult height; 95% CI: 2.83 to 6.21 and 4.48 to 7.52; $p < 0.001$ and < 0.001 , respectively), with significant heterogeneity for two height SDS comparisons, and effect-size estimates were more obvious when combined with growth hormone. There was a low probability of publication bias for above comparisons, as indicated by Egger's tests. Subgroup and meta-regression analyses revealed that intervention interval, treatment regimen and percentage of boys were potential sources of between-trial heterogeneity.

Conclusions: Our findings indicate that GnRHa are effective to treat short stature children with normal puberty, especially in combination with growth hormone, which supported our hypothesis that GnRHa can increase final height in children with short stature. Moreover, our subgroup and meta-regression analyses revealed that intervention interval, treatment regimen and percentage of boys were potential sources of between-trial heterogeneity.

P3-293**Clinical evolution of a patient with isolated growth hormone deficiency type IA treated with rIGF1 for 5 years after the development of GH-antibodies**

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Introduction: Isolated growth hormone deficiency (IGHD) type IA causes a severe growth retardation. Their initial good response to exogenous GH is hampered by the development of anti-GH-antibodies leading to treat with IGF1 as the only therapeutic option. Here we present the evolution of a patient with IGHD type IA treated with IGF1r for more than 5 years.

Description of the case: We present a 5-year-old patient from Pakistan, without previous anthropometric data. Height 74.2cm (-8.93 DE), weight 9kg (-4.48 DE), normal segmental proportions, truncal obesity, small face and broad forehead, micro-penis, bilateral cryptorchidism and acute voice bone, healthy consanguineous parent (mother's height 158cm, father's height 168cm), 3 brothers with normal height.

Complementary tests: bone age was 2.5 years, Karyotype: 46XY. IGF1: 41.3 ng / ml (-1 DE). Basal GH test 0.24 ng / ml, peak 0.28 ng / ml. The other hormonal studies were normal. Testicular ultrasound: testicles in the inguinal canal (1.5cm). Brain MRI: adenohypophysis hypoplasia. The genetic study showed an absence of the GH1 gene in homozygotes the.

Evolution: Treatment was started with GH (0.04 mg /kg /day) with good response during the first 6 months: height velocity (HV): 7.74 cm/year, IGF1 185 ng / dl (+ 1.15DE). Subsequently, a poor response was observed with decrease in HV (4cm/year) and undetectable IGF1 (baseline and after IGF1 generation test). The study of anti-GH-antibodies was positive at 1: 10000 dilution.

After these results, treatment with GH was suspended and began treatment with rIGF1 (40 mcg /kg /day in progressive increase up to 120 mcg /kg /day). Previously complementary studies (ECG, echocardiography, abdominal ultrasound, carotid ultrasound, retinography and audiometry) were performed and were normal. The capillary glycemia also were monitored and was always in normal ranges.

The patient showed a good evolution of height. Currently the patient is 12 years old and after 5 years of treatment with rIGF1 his height is 118.6 cm (-4.88 SD) and he maintains a HV of 6.87 cm/year, no adverse effects associated with the treatment were observed, except an increase in BMI during the first 3 years of treatment that required dietary support.

Conclusions: Treatment with recombinant IGF-1 for 5 years has shown good results in our patient with GH deficiency type IA, without adverse reactions except an increase in BMI that has occurred in the first years and has been controlled with dietary measures.

P3-294**Beck Depression inventory scores for children with some chronic diseases (Type I diabetes mellitus, Sickle cell anaemia, and AIDS) in University of Port Harcourt Teaching Hospital**

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Objectives: To determine the presence of depressive disorders in adolescents with T1DM, SCA, and HIV/AIDS being managed in UPTH and to compare the scores between the various diseases.

Method: A cohort study of 75 children (20 T1DM, 26 SCA, and 29 HIV/AIDS) presenting to the Department of Paediatrics, UPTH between 1st of October 2018 and 31st of May 2019 had an interviewer administered Beck depression inventory questionnaire given to them, after obtaining informed consents from their parents and ascents from the children.

Total scores were collated for each patient and means with SD for each disease category were compared using ANOVA, and a post hoc analyses done between 2 different diseases. A Pearson's correlation test was used to compare relationships between Depression scores and independent variables and in all statistics, a p value <0.05 was set as significant.

Result: Of the 75 children (20 T1DM, 26 SCA, and 29 HIV/AIDS), 43 males (57.3%) and 32 females (42.7%) $\chi^2 = 11.656$, $p = 0.003$. The mean age was 14.06 ± 2.57 and most of the children were in the middle social class 48, with 13 in the high class and the difference was significant, $\chi^2 = 31.76$, $p < 0.001$. Twenty-eight (37.3%) of the patients had scores in the depression range; 15 in moderate depression and 13 in clinical depression. The children with SCA had the highest mean scores 16.19 ± 6.76 , while those with T1DM had the lowest 12.30 ± 5.42 , though the difference in means between all groups was insignificant, $p = 0.101$. The mean BDI scores between socioeconomic classes was lowest in the high class (13.15 ± 5.81), and highest in the low class (15.07 ± 4.63), but the difference was not significant, $F = 0.296$, $p = 0.744$. Twenty-six patients had suicidal thoughts, and 2 of these agreed they would like to do it.

Conclusion: Twenty-eight (37.3%) of the study population had depression and children with sickle cell anaemia had higher mean BDI scores than those with T1DM and HIV/AIDS. Though none of the patients with BDI scores in the depressive range was severe, this screening tool afforded them the opportunity for psychological reviews. Periodic psychological evaluation of children with chronic diseases is advocated to screen those with depressive symptoms and commence treatment immediately.

P3-295

A Novel Pathogenic Mutation of Vitamin-D-dependent Rickets

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Background: Vitamin-D-dependent rickets 1A (VDDR-1A) is a extremely rare, autosomic recessive genetic form of rickets caused by a defect in vitamin D 1 α -hydroxylase enzyme which leads to low levels of 1,25-(OH) vitamin D.

Herein, we report two Moroccan sisters R.E. and N.E. (respectively 3 and 15 months old), born from consanguineous parents, who presented with psychomotor retardation and failure to thrive.

Methods: Biochemical analyses in serum and urine were conducted using the automatic analyzer Cobas immediately after collection. Serum intact PTH was measured by chemiluminescence assay. 25-OH vitamin D and 1,25-(OH) vitamin D levels were measured by enzyme immunoassays.

The entire coding region of CYP27B1, CYP2R1 and VDR genes were sequenced through NGS technology. Relevant genetic variations were resequenced through Sanger technology. The in silico prediction models used were Polyphen2, SIFT, MutationTaster, PHRED, MutationAssessor.

Results: Both sisters showed typical laboratory findings of VDDR-1A including hypocalcemia, hypophosphatemia, elevated ALP and PTH. Further assessments demonstrated normal-elevated levels of 25-OH vitamin D with low 1,25-(OH) 2 vitamin D.

Radiological workup revealed osteopenia, widened and irregular epiphyseal plates and in the older sister rachitic rosary.

We therefore sequenced the entire coding region of genes that has been associated to this clinical condition. Both sisters showed the homozygotic mutation p.Leu169Pro (c.596T>C) of CYP27B1 gene that has never been described before. All prediction models consider this mutation harmful.

Both sisters immediately started 1,25-(OH) Vitamin D supplementation (N.E. took a galenic formulation of Calcium too).

They both showed an adequate but incomplete treatment response with psychomotor retardation improvement, weight gain, normalization of serum Ca and P levels and a significant decrease of PTH and ALP levels.

Conclusion: We report a novel pathogenic mutation of CYP27B1 that leads to VDDR-1A.

An early diagnosis is necessary to prevent serious complications of rickets that are only partially reversible.

P3-296

Neonatal severe hyperparathyroidism - using genetics to determine treatment

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Background: Disorders of the calcium sensing receptor (CaSR) cause hyper- and hypo- calcemia, depending on the location and type of mutation. Familial hypocalciuric hypercalcemia is a benign disorder in which calcium levels are slightly elevated in the presence of slightly elevated parathyroid hormone (PTH). Neonatal severe hyperparathyroidism (NSHPT) is a rare life-threatening disorder in which there are high levels of calcium accompanied by high levels of parathyroid hormone.

Most cases of NSHPT are autosomal recessive and caused by homozygous mutations of the CaSR gene.

Calcimimetic drugs such as cinacalcet enhance calcium's effect on the CaSR. Cinacalcet has been shown to help regulate calcium levels in some children with NSHPT.

Case: A female baby born at 39 weeks of gestation, 3.2 kg via normal vaginal delivery. After birth she displayed respiratory distress, a small bell-shaped thorax and multiple rib fractures, osteopenia, and osteodysplasia. Serum calcium was 11mg/dl (norm 8.5-10.5) but PTH was 1590 pg/ml (norm up to 65). Urine calcium was low. Serum calcium rapidly rose up to 15 mg/dl and she received one dose of pamidronate 0.5mg/kg with a good response. Cinacalcet was added as calcium continued to rise, until calcium stabilized at 12.5 mg/dl. PTH remained extremely elevated - over 1100 pg/ml. Due to high calcium levels and no reduction in PTH, she underwent total parathyroidectomy. At four months she is still hospitalized, and still depends on nasogastric tube for feeding. She is on calcium and vitamin alpha-D3 supplementation with stable serum calcium levels.

Genetic testing is positive for a homozygous CaSR mutation (c.659G>A, pp Arg220Glu). This mutation has only once been described in FHH. Her mother has FHH and is heterozygous for the mutation, but her father is normocalcemic and does not carry a mutation on the CaSR gene. Possibly, the baby has maternal uniparental isodisomy and has inherited both mutations from the mother. There might be a deletion on the paternal allele. We are now completing genetic testing.

The missense mutation in the CaSR gene (c.554G>A, p.R185Q), is a known pathogenic mutation causing NSHPT and is responsive to cinacalcet. Other mutations described are not responsive. Knowing the mutation can facilitate treatment choices.

Conclusion: We describe a rare case of neonatal hyperparathyroidism with a formerly undocumented homozygous mutation. This mutation can shed light on novel modes of inheritance for this rare disease and better understanding of treatment modalities for this disease.

P3-297

Liver Transplantation in Saudi Homozygous Familial Hypercholesterolemia Patients

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Introduction: Patients with homozygous familial hypercholesterolemia (HoFH) suffer from this disorder from birth and they have abnormally high cholesterol levels due to a disease that has autosomal dominant inheritance of genetic aberrations in the coding region for low density lipoprotein receptors (LDLR) in more than 90% of cases, other gene defect includes mutations in apolipoprotein B100 (apoB100) and proprotein convertase subtilisin/kexin type 9 (PCSK9). Many modalities have been used for the treatment of (HoFH) patients including diet, drugs, LDL apheresis, and portacaval shunts. The effectiveness of these therapeutic regimens has shown limited efficacy in reducing the total cholesterol and LDL cholesterol in plasma and only provide temporary solutions for hypercholesterolemia, Previous researches has demonstrated that liver transplantation was a highly effective means to lower the LDL cholesterol level.

Methodology: Retrospectively, we analyzed 17 pediatric patients under the age of 15 years old who had been diagnosed with (HoFH) confirmed by biochemical ± genetic results in the Kingdom of Saudi Arabia. The total cholesterol and (LDL) cholesterol of 17 patients were tested upon initial presentation and compared to the results of lipid testing performed after administration of drug treatment therapy, and then again following liver transplantation.

Results: The results indicated that after the administration of drug therapy, total cholesterol levels decreased by an average of 3.79 mmol/l or 15.16%, and LDL levels decreased on average by 2.72 mmol/l or 12%. However, three values showed an increase from pre-drug treatment values. In contrast, patients' lipid values that were measured following liver transplantation had significantly declined to within normal limits for most patients. Post-transplant total cholesterol values had declined by a mean of 19.96 mmol/l or 81%. The levels of LDL in the post-transplant HoFH patients had experienced a mean decrease of 17.48 mmol/l or 84%. All statistical results were found to be significant with p values < 0.02.

Conclusion: These findings suggest that liver transplantation provides a more effective means in reducing total cholesterol and LDL in HoFH patients. Although liver transplantation is the better treatment for elevated cholesterol, risks, complications, and a shortage of donor organs may present problems.

P3-298

Mitchell-Riley Syndrome, a report of novel mutation in a Palestinian family resulting in Neonatal diabetes

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Introduction: Mitchell Riley syndrome is a rare autosomal disorder, characterized by severe neonatal diabetes associated with hypoplastic or annular pancreas, duodenal or jejunal atresia, intestinal malrotation, gallbladder hypoplasia or agenesis, and cholestatic disease, less common features were reported such as severe neonatal anemia, hemochromatosis and biliary atresia.

Mitchell-Riley syndrome is caused by a mutation in regulatory factor X (RFX), mutations in RFX6 are assumed to be the cause of neonatal diabetes in this syndrome.

Here we report a novel mutation of RFX6 gene in a Palestinian infant with Mitchell Riley syndrome.

Case presentation: We report a female newborn, for a consanguineous Palestinian parents, fetal ultrasound revealed intrauterine growth restriction, mild polyhydramnios and findings suggestive of duodenal atresia (double bubble sign). She was born at 38 weeks of gestation, birthweight 1705 gm. Initial abdomen x-ray showed classic double bubble sign, and was operated at 4th day of life. Then developed hyperglycemia 330 mg/dl and clinical picture suggestive of neonatal diabetes.

During hospitalization developed clay colored foul smelling diarrhea was soon noticed, several measures were taken to improve feeding tolerance including hydrolyzed, elemental formula, monogen -MCT rich formula- as well as chicken soup however non proven to be beneficial to improve baby failure to thrive and she remained dependent on total parenteral nutrition.

Molecular data: Sequencing of the RFX6 gene of the patient revealed a novel homozygous mutation C.1278 1281delTCTT in exon 12 of RFX6 gene. Father and mother were heterozygous for the same mutation.

Conclusion: To the best of our knowledge this is the seventeenth proband with Mitchell-Riley syndrome worldwide, and the first description of this disease in a Palestinian family with molecular confirmation allowing accurate genetic counseling, early diagnosis of affected kindreds, early therapeutic interventions and avoiding complications.

P3-299

Review of neonatal cortisol evaluation between 2012-2018 in a single centre: trends, outcomes and associations

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Background: Neonatal cortisol assessment is indicated in suspected adrenal insufficiency. Clinical presentation includes: low blood glucose, low blood pressure, ambiguous genitalia, electrolyte abnormalities, midline abnormalities.

Aims: Review the trends, outcomes and associations of cortisol assessment in neonates within our Trust between 2012–2018.

Objectives:

Review:

- trends in cortisol assessments
- indications for 'random/serial' cortisol tests.
- Indications/outcomes for Synacthen tests
- relationships between gestational age (GA), birth weight (BW) and cortisol assessment.

Methodology: Cortisol tests performed on neonates (≤ 30 days age) at our Trust, over 7 years: 2012–2018 (inclusive) were retrieved. We identified random/serial ('screening cortisol') versus cortisol done as part of Synacthen tests.

We looked at trends for testing, and further data collection was done as follows:

- screening cortisol: Indication, number of tests, outcomes.
- Synacthen tests: Indication, type of test [short Synacthen test (SST) vs low dose Synacthen test (LDST)], results, short and long term outcomes, relationship to BW/GA.

Results: There were 412 cortisol tests over the 7 years, in 172 patients. Numbers were stable between 2012–2014, but between 2015/2016 and 2017/2018 there was a significant increase in overall cortisol tests= 230%; and Synacthen tests=430%. This was not comparable to stable admission rates: 1997 patients over 2015/2016 and 1916 in 2017/2018.

There was no significant relationship between premature versus term deliveries and abnormal Synacthen tests ($p=0.32$); or between BW (i.e. SGA vs AGA) and abnormal Synacthen tests ($p=0.67$).

Summary/Conclusions: There is an exponential increase in cortisol assessments, out of keeping with changes in admission rates. However 91% of testing indications were appropriate. Pick-up of adrenal insufficiency was low: 6%. Subsequent reassessment of adrenal function is imperative as 64% of these results were transient. There were no associations between BW or GA and abnormal Synacthen results.

Table 1: Screening cortisol versus Synacthen tests.

	Screening cortisol	Synacthen tests
Number of patients	143 (=83%)	29 (=17%)
Split	66.4% (n=95): <u>single</u> screening cortisol level.	72.4% (n=21/29) were SSTs.
	33.6% (n=48): <u>2 or more</u> screening cortisol levels.	27.6% (n=8/29) were LDSTs.
Top 3 indications:	Hypoglycaemia(35.6%), ambiguous genitalia(16%), conjugated jaundice(9%).	Hypoglycaemia(44.8%), ambiguous genitalia(6.9%) and hyponatremia(6.9%).
Outcomes:	Only ONE patient was started on treatment based on just the screening results. Subsequent Synacthen test confirmed adrenal insufficiency.	38% of the initial Synacthen tests were abnormal (n=11/29). Of these only 36% (n=4/11) remained on treatment after age of 2 years: Dx=2x Hypopituitarism + 1x Hypoglycaemia, SGA and maternal pre-eclampsia +1 Preterm.

P3-300

Height and Upper/Lower Body Ratio in Turner Syndrome Adolescents in Indonesia; Is There Any Significant Difference Based on Karyotype?

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Background: Short stature is one of the most common findings in Turner syndrome. There are two types of Turner syndrome based on karyotype: classical and mosaic. It is often marked by the body disproportion and dysmorphic profile of the patients. There are still not many data available regarding upper lower body segment ratio (U/L body segment ratio) in Turner syndrome patient in Indonesia. This study aims to show the profile of height and U/L body segment ratio and whether there is any significant difference based on their karyotype in Turner syndrome patients in Indonesia.

Methods: Samples were taken from Endocrine Out-Patient Clinic at Cipto Mangunkusumo National Hospital. Weights, heights, and sitting heights were measured. The heights were plotted into CDC growth curve and Turner syndrome growth curve. The upper-lower body segment ratio was measured and plotted into the U/L body segment ratio curve. The significance of the difference in the height and the U/L body segment ratio between classical and mosaic karyotype were measured using independent T test.

Results: Out of 21 samples, 8 were having classical karyotype and 13 were having mosaic karyotype. Seven of these received growth hormone (GH) and 14 did not. Six of the subjects who received GH were having short stature. Almost all of the subjects

were having short stature (85.7%) based on CDC growth curve (<3 percentile CDC curve), except for 2 subjects with mosaic karyotype (both subjects were at 7 percentile CDC curve) and 1 subject with classical karyotype (at 4 percentile CDC curve) with normal height (14.3%). Two of these subjects did not receive growth hormone (GH). The upper-lower body ratio in all samples was increased. There was no significant difference of the U/L body segment ratio ($p > 0.05$) and height ($p > 0.05$) between classical and mosaic karyotype.

Conclusion: Short stature was found in 85.7% of the subjects. The upper/lower body ratio in adolescents with Turner syndrome in Indonesia was found to be increased. Body height and U/L body segment ratio were not significantly different between classical and mosaic karyotype. In this study, apparently, subjects who obtained GH therapy were still unable to attain a normal height and a normal U/L body segment ratio.

Keywords: karyotype, upper lower body segment ratio, height, growth hormone therapy

P3-301

A novel heterozygous mutation in the SLC5A2 gene causing mild failure to thrive and subclinical hypoglycemia in a 2-year old girl

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Patients: A 2-year old girl was referred due to glucosuria 1874 mg/dl. Fasting blood sugar was 71 mg/dl and HbA1c 4.8%. Examination of her growth charts revealed mild failure to thrive, since 15 months of age, as far as weight gain and height velocity. We used Flash technology (FreeStyle Libre) to identify hypoglycemic episodes. In 9 days, 8% of the time was < 70 mg/dl, with 11 hypoglycemic events: mean duration 94 min, lowest 52 mg/dl.

Treatment: We started the child on cornflower 1 g/Kg, with her milk at bedtime and advised for frequent feedings every 3-hours during the day. There was significant improvement in height velocity and weight gain within the next semester, with the BMI completely normalizing. HbA1c did not change but subsequent Libre scans showed elimination of all hypoglycemic excursions.

Methods: We decided to sequence the SLC5A2 gene, as most probable genetic cause. Genomic DNA extracted from peripheral blood. The sample was analyzed using the SeqCap EZ HyperCAP Library (Roche), followed by next generation sequencing (IlluminaNovaSeq 6000). The bioinformatics analysis has been performed using software packages (bcftofastq version 2.20, Isaac Aligner version 4, GATK "Genome Analysis Toolkit" version 4, Samtools version 1.9 and Bedtools version 2). Data analysis and interpretation were done based on patient's clinical information and filtered for a requested gene panel. Variants with a minor allele frequency greater than or equal to 1% were not evaluated. Variants in genes lacking evidence of clinical significance and variants in genes unrelated to the patient's characteristic were not evaluated, unless present in genes assessed for medically actionable secondary findings, in accordance with ACMG recommendations.

Results: The following nucleotide variant is reported: c.[1021+1G>A]+[=] exon 8 in SLC5A2 gene. Variant c.1021+1G>A in heterozygous state is identified in exon 8 in SLC5A2 gene; this variation causes the elimination of canonical splice site. This variant has not a resident no frequency data are reported (gnomAD, dbSNP, ExAC). The variant is not reported in scientific literature and in ClinVar. Mother was also carrier but with no glucosuria.

Conclusions: Heterozygous mutations in the SLC5A2 gene may cause subclinical hypoglycemia and mild failure to thrive in early infancy. Given the mother's state, this novel mutation may be behaving as dominant in early infancy, or there may be an imprinting mechanism involved. Early detection and treatment of this rare disorder may prevent neurological sequelae of undetected hypoglycemia while restoring weight gain and height velocity.

P3-302

Cognitive and Learning Performance of Children and Adolescents Cancer Survivors

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Objective: The aim of this study was to compare the sociodemographic and cognitive profile, the learning performance and symptoms of attention deficit hyperactivity disorder (ADHD) of children and adolescents survivors of pediatric cancer to those of healthy controls.

Methods: Thirty survivors of pediatric cancer and thirty age-matched controls (mean age \pm SD 11.7 \pm 2.7 years, 46.0% boys, 54.0% girls) were evaluated with the Wechsler Intelligence Scale for Children (WISC-III), the validated LAMDA (software for screening for learning abilities, disabilities and weaknesses) and the ADHD Rating Scale. Sociodemographic data were also assessed.

Results: General intelligence of controls (mean \pm SD 107.3 \pm 18.1) was significantly ($P = 0.027$) higher than the average general intelligence of cancer survivors (mean \pm SD 97.5 \pm 21.4). Analysis of the results of the WISC-III subscales revealed statistically significant differences in the verbal scale ($P = 0.041$), with higher scores of the controls (mean \pm SD 53.8 \pm 10.2) compared to the cancer survivors (mean \pm SD 48.3 \pm 14.2). No statistically significant differences between controls and cancer survivors were found in the

performance scale. The LAMDA test revealed statistically significant differences in grammar ($P = 0.012$) and syntax ($P < 0.001$), with the controls achieving higher scores in the respective fields.

Regarding the ADHD symptomatology, no significant differences were noted between cancer survivors and controls. Furthermore, for the total study sample, the subscales of the ADHD questionnaire demonstrated no correlation with either the subscales of the WISC-III test, or the subscales of the LAMDA test.

Finally, children and adolescents whose parents had higher levels of education, demonstrated significantly higher general intelligence scores in WISC-III ($P = 0.026$). More specifically, higher scores were observed in the verbal scale ($P = 0.024$) and also in the information ($P = 0.001$), similarities ($P = 0.014$) and vocabulary ($P = 0.019$) subscales. In the LAMDA learning test, in the category of stimuli identification accuracy, higher ($P = 0.016$) scores were achieved by children and adolescents who had at least one parent of higher educational background.

Conclusion: In this small study sample, children and adolescents with a history of pediatric cancer demonstrated lower intelligence quotient and lower performance in some learning domains (grammar, syntax) than controls. Higher intelligence and learning scores were detected in the participants with parents of higher educational level. Larger studies are needed to confirm these findings.

P3-303

Hirsutism in children: pitfalls and diagnostic challenges

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Introduction: Hirsutism is a condition defined as excessive male-pattern hair growth in females most commonly caused by hyperandrogenism. Polycystic ovary syndrome (PCOS), non-classic adrenal hyperplasia (NCAH) due to 21-hydroxylase deficiency and androgen-secreting tumors represent causes of androgen excess. Common features such as hirsutism, polycystic ovaries, oligomenorrhea or amenorrhea, and insulin resistance make it hard to distinguish between the first two conditions.

Material and methods: A retrospective study was conducted at "Louis Turcanu" Children's Clinical and Emergency Hospital over two years. Twenty-three female patients admitted to the Endocrinology Department for hirsutism were included. Patient history and physical examination, blood sampling, ovarian sonography, oral glucose tolerance tests were performed in all patients. Insulin resistance (IR) was assessed by the homeostasis model assessment (HOMA).

Results and discussions: Sixteen patients were diagnosed with PCOS according to the Rotterdam criteria, and seven patients were diagnosed with NCAH. Obesity, defined as a BMI at or above the 95th percentile, had a higher prevalence among PCOS patients compared to NCAH patients; 52.9% obese PCOS patients compared to 33.3% obese NCAH patients. IR was diagnosed in 56.2%

of PCOS patients. Oligomenorrhea was more frequent among pubertal patients with PCOS (31.2 %) compared to NCAH (14.2%). The highest mean DHEA levels were found in NCAH patients, 15.55 ± 7.816 , 95% confidence interval [CI] compared to 12.7455 ± 6.027 , 95% CI in PCOS patients. Basal 17-hydroxyprogesterone levels >2 ng/mL were more prevalent in the NCAH group, whereas an LH/FSH ratio > 2 was predominant among PCOS patients.

Conclusions: Differentiating between PCOS and NCAH remains a diagnostic challenge. Basal 17-hydroxyprogesterone levels >2 ng/mL and LH/FSH ratio > 2 , are useful markers to distinguish between the causes of androgen excess. Further, more extensive studies and genetic testing are needed.

P3-304

Congenital craniopharyngioma - A rare case of congenital hypopituitarism

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Introduction: Hypopituitarism leads to one or more pituitary hormones deficiency. Hypopituitarism can be congenital or acquired. The incidence of congenital hypopituitarism is between 1 in 4000 and 1 in 10 000 live births. Children with congenital hypopituitarism may present with hypoglycemia, hyponatremia, shock, micro phallus in males, and later present with growth failure. It can be due to congenital or acquired causes. Adamantinomatous type craniopharyngioma is a relatively rare childhood tumor with the prevalence of 6%- 10% of all intracranial tumours. Even though craniopharyngioma is a childhood tumor, embryonic cell proliferation can occur even in the antenatal period. Congenital craniopharyngioma is a very rare suprasella brain tumour which constitute around 0.5-1.5% of all congenital tumours. Tumour location and its pressure effects lead to pituitary hypo function and visual disturbance. Nine cases of antenatally diagnosed craniopharyngiomas have been reported in the literature. We report the first case of congenital craniopharyngioma in Sri Lanka presenting with hypopituitarism.

Case History: A Baby boy was referred due to micro phallus. He had uncomplicated antenatal period. His birth weight was 2.9 kg. He had neonatal jaundice. There was no hypoglycemia. Occipitofrontal circumference was in the fiftieth centile. He didn't have midfascial hypoplasia. Eye examination was normal. His phallus was 2cm with bilateral hypoplastic scrotal sacs with atrophic small testis.

Biochemical investigations revealed multiple pituitary hormone deficiency. Leutinizing hormone (LH) and follicular stimulating hormone (FSH) were low. In addition, he had low basal cortisol (22nmol/l) with poor response to short synacthen test. But his thyroid functions were normal. He was started on oral hydrocortisone replacement therapy. MRI brain was scheduled at the age of 1 year.

At 11 months he presented with features of increased intracranial pressure. MRI brain showed solid and cystic mass involving the sella and suprasella region with obstructive hydrocephalus.

Pituitary gland and optic chiasma were not separately seen. He underwent excision of the craniopharingioma. Following surgery he needed multiple pituitary hormones replacement. He had developmental deterioration and visual impairment post operatively. Radiotherapy was not given due small age.

Conclusion: This case highlights the very rare congenital cause of hypopituitarism. Antenatal and early postnatal imaging with the ultra sound brain would help in the early diagnosis. Total resection is the treatment modality. Even with improving neurosurgical technology, prognosis is poor due to the age, size and location of the tumour. Congenital craniopharyngioma leading to hypopituitarism need coordinated care with multiple specialties.

P3-305

Combined Surgical and Medical Treatment in an Adolescent with Severe Gynecomastia Due to Excessive Estradiol Secretion: A case report

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Background: Gynecomastia develops due to the reversed estradiol-to-Testosterone ratio in adolescence, and symptoms typically improve within two years. The causes vary widely, including estrogen excess and tumors, and surgical treatment is usually given in late adolescence because postoperative symptoms may recur in adolescents. There are no guiding recommendations for gynecomastia to date besides the suggestion to consider rapidly growing gynecomastia and breast tissue ≥ 4 cm as the pathologic condition. Therefore, this study reports a case of a pediatric patient with severe gynecomastia due to excessive estradiol secretion who showed a positive outcome after receiving surgical treatment combined with aromatase inhibitor administration. The study includes clinical and laboratory results from his first visit at 9 years and 3 months of age to last postoperative follow-up at 15 years of age, as well as the postoperative course of outcomes.

Case Presentation: A 9-year old boy visited to the Department of Pediatric Endocrinology for breast budding. At that time, the patient showed breasts at Tanner stage II and no abnormality on hormone tests. During a follow-up, both gynecomastia had progressed to Tanner stage III-IV at age 13. Tamoxifen 10 mg bid was administered; however, the condition rapidly progressed to Tanner stage V at 13.5 years. The evaluation of pathologic gynecomastia showed an increase of estradiol to 296 pg/mL(reference range[R]: 10-36) and microlithiasis in both testes. As the condition worsened, total mastectomy was performed at the age of 13.5 years while minimizing surgical scarring using the peri-areolar approach. In two months, there was some improvement in breast enlargement, but the progression of breast budding was also observed along with the elevation of estradiol to 535 pg/mL. Based

on the assessment that elevated aromatase activity had induced breast budding, we changed the medication to anastrozole (Arimidex) 1 mg once a day, after which the estradiol level improved to 38.5 pg/mL and was maintained well in the two-year postoperative follow-up.

Conclusions: This case report shows a combined plastic surgery and appropriate medical management bring a positive outcome in severe gynecomastia patient, and it suggests a need for endocrine screening in pediatric gynecomastia patients.

P3-306

Improvement of Metabolic Control in Children with Type 1 Diabetes Using Continuous Glucose Monitoring Devices

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Introduction: Achieving metabolic control in children with type 1 diabetes (T1DM) is not an easy task. Despite the new profiles of insulins and therapies with continuous infusion, hypoglycemia continue to be the most important barrier that prevents us from correctly controlling these patients.

Close control of capillary glycaemia is important for treatment adjustment. This self-control provides us with static information about capillary glycemia at a specific time, and multiple daily controls are necessary to know the patient's glycemic profile. It is demonstrated that the greater number of capillary controls there is an improvement in HbA1c.

Some technologies have been developed, and provide us information in real time of the patient's glycemic profile, using interstitial glycemia data, which, in times of stability, can be equivalent to capillary blood glucose values. They also provide personalized alarms for each patient, allowing them to make quick decisions, they also can reduce the number of hypoglycemia and increase the degree of involvement of the patient in their day to day.

Material And Methods: Study of the effect on metabolic control (A1C) using continuous glucose monitoring devices in pediatric patients with T1DM.

We studied average A1C in the last 6 months in 182 pediatric patients, among which there is a group with continuous monitoring (Guardian®, Dexcom®, FreeStyle®) and another group with capillary blood glucose self-monitoring. In both groups there are patients in treatment with multiple doses of insulin and patients with continuous subcutaneous insulin infusion.

Performed the statistical analysis with the SPSS 19 program, comparing HbA1c means from the Levene test.

The average A1C is studied in a group of patients with continuous glucose monitoring (CGM) ($n = 110$) and compared with the average A1C in the group of patients without monitoring ($n = 72$) and as a result, there is a significant HbA1c lower in the group of patients with monitoring (7.47 vs 7.88, $p < 0.05$). In addition, among patients with monitoring, A1C is lower in patients who use continuous subcutaneous insulin infusion (7.15 vs 7.68, $p < 0.05$).

Conclusions: In our group of patients we can see that the use of continuous glucose monitoring improves the metabolic control in

pediatric patients, and this control is optimized when we associate a continuous glucose monitoring device with an infusion system of subcutaneous insulin.

P3-307

Autoimmune thyroiditis in beta thalassemia major after the hematopoietic stem cell transplantation - case report

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Introduction: Beta thalassemia is a common genetic disorder in Mediterranean countries. Congenital hypothyroidism is also a condition resulting with deficiency of thyroid hormone in newborn infants. Autoimmune thyroid dysfunction in childhood patients with thalassemia major is uncommon and poorly described. We report a case of a child with two independent diseases - clinical hypothyroidism diagnosed in early childhood, and beta thalassemia major who developed autoimmune thyroiditis with unusual acute thyroid dysfunction.

Case presentation: We present a 13-year-old boy with beta thalassemia major and clinical hypothyroidism diagnosed in infantile period. The child received regular L-thyroxine therapy and multiple transfusions together with chelation therapy. Haploidentical transplantation of hematopoietic stem cells from his mother was performed two years ago. Since then, patient was put on immunosuppressive therapy. In January 2019, he represents with anterior neck pain and fever. Clinical exam showed periorbital swelling. Laboratory evaluation of the thyroid function revealed increased FT4 levels ($>77.2 \text{ pmol/L}$) and decreased TSH levels (0.029 uIU/ml), explaining the thyrotoxic crisis with hormonal discharge. Thyroglobulin antibodies were extremely elevated (2168 IU/ml). The pneumoslide was positive for Adenovirus IgG. Acute autoimmune thyroiditis due to the viral infection in immunocompromised child was diagnosed. The thyroxine replacement therapy was temporarily stopped, after several weeks the therapy was given gradually until TSH level become normal.

Conclusion: Although the simultaneous occurrence of beta thalassemia major, acute and autoimmune thyroiditis in patient on thyroxine replacement therapy can be coincidental, this combination is rare in childhood. To the best of our knowledge, there is no evidence about a plausible association between the acute autoimmune thyroiditis and immunosuppressive therapy given after transplantation. This type of thyroiditis can be overlooked and early diagnosis is important to correct the negative systemic effect of thyroid dysfunction. Follow up of thyroid function in transplanted children that have received immunosuppressive therapy is mandatory.

P3-308

Grave's disease: what place in the child's hyperthyroidism?

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Background: Hyperthyroidism is a condition rarely found in children. In the majority of cases, it is a Grave's disease whose clinical expression is very similar to that observed in adults.

Objective: describe the clinical, evolutionary and therapeutic epidemiological features in children with hyperthyroidism and especially Grave's disease.

Materials and methods: This is a retrospective study of 25 cases of hyperthyroidism, performed at the endocrinology department of C.H.U. of Oran over 10 years,, the statistical analysis is carried out on the software Epi info 6.fr.

Results: There were 25 cases including 22 children and 3 adolescents, the sex ratio is 0.08, the average age is 13.2 ± 2.3 years. The family history of thyroid pathology is found in 52% of cases. Goiter is the main reason for consultation. The symptomatology is dominated by goiter and tremor (100%), thermophobia (92%), tachycardia (76%). Exophthalmos is found in 60% of cases. There are signs of compression in only 8% of cases. Hyperthyroidism is biologically confirmed in all patients and Graves' disease ranks first among 84% of cases. All patients were treated with synthetic antithyroid drugs: 10 cases were operated, 1 case underwent Radioactive Iodine Therapy and 2 cases were in remission.

Discussion: Hyperthyroidism especially affects the older child with a female predominance. The positive diagnosis is established by the hormonal assessment. Graves' disease is the most common etiology. The majority of patients are treated with synthetic antithyroid drugs. Remission is less common in children than in adults. Thyroidectomy and radioiodine therapy are the two therapeutic alternatives.

Keywords: Hyperthyroidism - Graves - Children - Adolescents - Oran.

P3-309

Vitamin D status among children and adolescents in an Egyptian cohort: can we predict vitamin D deficiency?

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Background and Aim: Vitamin D plays a crucial role in skeletal and extra-skeletal physiology. It is essential for growth, development and health. It works as a paracrine and autocrine signaling molecule that affects nearly all systems in the body. Vitamin D deficiency (VDD) is prevalent in many countries in all age groups, and may be overlooked due to the variable clinical presentations according to age. This study was conducted to assess vitamin D

status among children and adolescents and to find out predictors of vitamin D deficiency or insufficiency among studied group

Methods: Cross sectional analytical study was conducted on 88 subjects (47 children and 41 adolescents), all participants were subjected to history, clinical examination, and estimation of serum vitamin D, alkaline phosphatase (ALP), calcium (Ca) and phosphorous levels. The subjects were divided into four groups according to serum vitamin D level; vitamin D severely deficient <10 ng/ml, vitamin D deficient 10 -20 ng/ml, vitamin D insufficient 20 - 30 ng/ml and vitamin D sufficient > 30 ng/ml

Results: VDD was prevalent in the studied group where 58% of them showed vitamin D deficiency (10% of them were severely deficient), 25% showed insufficiency and 17% had normal vitamin D levels. Children showed 46.8% deficiency, 8.6% severe deficiency and 31.9% insufficiencies while the adolescents showed 48.8% deficiency, 21.1% severe deficiency and 17.7% insufficiency. The most evident predisposing factors for VDD were BMI and inadequate sun exposure. Muscle cramps were significant among children only. Multivariable linear regression analysis revealed that BMI ($p=0.01$) and fast food ($p=0.016$) were associated with increased risk of VDD.

Conclusions: Vitamin D deficiency and insufficiency are prevalent in Egyptian children and adolescents among both genders. Despite most of the cases were asymptomatic or presented with non-specific symptoms, obesity and fast food significantly affected vitamin D status among the studied group.

Keywords: *vitamin D, 25-OHD, deficiency, insufficiency, children, adolescents, obesity*

P3-310

Case Report: Primary Hyperparathyroidism Presenting as a Brown Tumor of Mandible in an Adolescent Girl - An Unusual presentation with Challenges and Outcome

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Brown tumor is a rare non-neoplastic focal giant cell lesion resulting due to increase osteolytic activity by excess of parathyroid hormone in cortical bone which is replaced by fibrovascular tissue, giant cells with hemorrhages and hemosiderin. It is a rare late stage bone sequelae of long standing hyperparathyroidism. Parathyroid adenoma is the commonest cause of primary hyperparathyroidism.

We present a referred case of 15-year-old girl with highly aggressive mandibular mass creating swallowing difficulties, oral bleeding episodes, and anterior mandibular erosion with dislodgement of teeth. The thorough clinical, biochemical, histopathology and comprehensive radiological assessment reveal parathyroid adenoma leading to a hyperparathyroid state leading to brown tumor. A rare presentation of long standing hyperparathyroidism was a challenge to treat with favorable outcome in poor resources. The main stay of treatment was removal of left upper parathyroid

adenoma resulting in reversal of metabolic de-arrangements but subsequent follow-up showed incomplete regression of tumor. Complete surgical excision of large disfiguring mandible residual and symptomatic mass was done successfully with osteotomy. No evidence of recurrence was observed in one-year follow-up. Thereafter reconstructive surgery of anterior mandibular bone was performed using alloplastic devices and bone grafts from cadaveric source and synthetic bone fragments. Alloplastic surgical membrane covered the whole augmented bone. After few months of optimized healing, restoration of incisors and canines teeth was done initially by placing artificial denture followed by permanent tooth implantation.

Such complications are rarely seen in presence of good medical standards and provision of advanced analytic facilities but still cases are encountered in underdeveloped countries with poor health facilities. The desirable aesthetic outcomes can only be produced with great expertise and can be achieved with biomaterial implants to replace, reconstruct and/or augment the tissue.

P3-311

Serum Calcium, 25(OH) vitamin D and Bone alkaline phosphatase in children with epilepsy receiving antiepileptic drugs in University of Port Harcourt Teaching Hospital

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Objective: The aim of this study was to analyse bone mineral status in children with epilepsy, on antiepileptic drugs (AEDs) regimen, using serum calcium, 25 (OH) vitamin D and Bone alkaline phosphatase (BALP) and compare these with age and sex matched controls.

Patients and Methods: This was a case - control study, conducted at University of Port Harcourt Teaching Hospital, from September 1 2018 to May 31 2019, with 200 (100 cases and 100 controls) participants, aged 1 - 18 years. Serum calcium, 25 (OH) vitamin D and BALP were analysed in children consecutively recruited using o-Cresolphthalein colorimetry for calcium, ELISA for BALP and 25 (OH) vitamin D. Student's t test was used to compare mean among cases and controls and correlation analysis to test relationships between variables.

Results: Serum calcium and vitamin D were significantly lower in cases, but BALP was higher ($P > 0.001$). Twenty two percent of cases were below normal vitamin D levels, as against 11% of controls ($p = 0.05$), while sixty two percent of cases had hypocalcaemia as against 27% of controls ($p > 0.001$). Cases receiving carbamazepine had lower vitamin D and calcium levels than those receiving phenobarbitone and sodium valproate, but those on sodium valproate had higher BALP. Children on polytherapy had lower vitamin D and calcium but higher BALP levels. Though not significant, there were negative correlations between BALP and vitamin D, but positive correlations between calcium and vitamin D and calcium and BALP.

P3-312**Emotional Status Instability and Body Mass Index as Predictive Markers for Dopamine System Dysfunction Evaluation in Pubertal Age Children**

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Study aim was to create a prognostic algorithm of dopamine system dysfunction in pubertal age children, based on emotional instability markers, depending on body mass index and pubertal periods.

Materials and methods: Study subjects comprised 120 children (11.6 – 17.9 y/o, the 2nd – 5th Tanner stages) from Belarusian population between 2015 and 2017. Emotional status instability signs were obtained using the Depression self-rating scale (DSRC). The depression development risk (total DSRC score) and depressive signs (no depression; one depressive episode; presence of depression) were evaluated. Corresponding to BMI SDS, patients were divided into: the 1st group - normal weight (NW) children, the 2nd one – simple healthy obesity (SHO) and the 3rd – extreme obesity (EO). Data were analyzed in mind to gender (male, female) and Tanner scale (early puberty (EP) and late puberty (LP) subgroups). Blood dopamine (D) concentration were detected in 88 patients using immunosorbent assay (ELISA). Agreeing with quartile measure of D levels, children were divided into: the 1st subgroup (low D concentration: < 10.9 pg/ml); the 2nd (moderately decreased concentration: 10.9–16.17 pg/ml); the 3rd (moderately increased levels: 16.17–19.3 pg/ml); the 4th (high concentration: > 19.3 pg/ml). Statistical analysis made by means of Spearman non-parametric correlations (r) and mathematical modeling methods ($p < 0.05$).

Results: We have got math model based on characteristics of emotional status instability and BMI, in the LP age children regardless of BMI. This model can use to predict the likelihood of dopamine system dysfunction in these subjects. For instance: a LP age patient with the presence of depression will have moderately decreased D concentration with 33.3% probability, moderately elevated - 16.7%, and high D levels - 50% ($p=0.016$). We had similar math model in adolescents with obesity. For instance: an obese adolescent with the presence of depression will have moderately reduced blood D level with 50% chance; moderately elevated D - in 33.3% and high neuropeptide in - 16.7% ($p=0.05$). Based on these two models, we created the prognostic algorithm for identifying of dopamine system dysfunction in adolescents.

Conclusions: Obtained prognostic math models could be used to evaluate dopamine concentration ranges based on the likelihood of depressive sins in obese adolescents ($p=0.05$) and in LP age patients ($p=0.016$) regardless of BMI. Based on the developed math models, we construct the diagnostic algorithm of dopamine system dysfunction, using BMI, puberty period and emotional status characteristics in adolescents.

P3-313**A Case Report of Persistent Hyperinsulinemic Hypoglycemia of Infant**

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Background: Persistent hyperinsulinemic hypoglycemia of infancy is the most common cause of persistent hypoglycemia in neonates and infants. It is a genetic disorder with both familial and sporadic forms. It is a clinically and genetically heterogeneous disorder, which ranges from life-threatening hypoglycemia presenting on the first day of life to only mildly symptomatic hypoglycemia in a child or adolescent that may be difficult to identify. The treatment of persistent hyperinsulinemic hypoglycemia is still a great challenge because the response to medical and surgical therapy varies.

Case: The patient presented here is a male infant who has preterm birth at 36 weeks 1 day and the birth weight of 4200g. After birth, he suffered from respiratory failure, neonatal infections and prolonged hypoglycemia accompanied by recurring seizures. The lowest plasma glucose concentration is 0,14 mmol/l. The plasma insulin concentrations measured twice as low plasma glucose was inappropriately elevated with 28 µUI/ml and 10.2 µUI/ml. Other laboratory tests in normal range. The diameters of head, body and tail of the pancreas are 9.6 mm, 3.4 mm and 4.8 mm one by one with several cysts on abdominal ultrasound. CT scan showed fatty liver and subcutaneous diffuse lipohypertrophy. Homozygous ABCC8 mutation (NM_000352.4 (ABCC8): c.3400-1G> A) was found. She was treated with diazoxide or maximum dose of somatostatin combined with nifedipine but did not respond. Because of his dependence on high-level intravenous infusion (> 10 mg/kg per minute), a near total (90%) pancreatectomy was performed. The pancreatic pathology confirmed congenital anomalies nesidioblastosis. After pancreatic resection, his plasma glucose condition improved significantly. So, he was discontinued medical therapy and discharged.

Conclusion: The patients who have homozygous mutations in ABCC8 gene often fail to respond to pharmacological therapy and require surgical therapy. Our patient has had a good response to a near total pancreatectomy. However, **18F-L-DOPA PET** was not performed before surgery. This limits the ability to investigate local or diffuse pancreatic lesion and suggestion for removing partial or near total pancreatic tissue.

P3-314**Case report: Hyperglycemic iperosmolar state in an obese prepubertal girl with newly diagnosis of type 2 diabetes**

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A 11years-old Italian severely obese prepubertal female (BMI: 32.4 kg/m²; SDS-BMI: 2.63) was admitted to the emergency

department due to worsening dyspnea and chest pain associated with severe polyuria, lethargy and lost weight from (85 kg to 78 kg in 7 days). She has history of severe hypertension treated with amlodipine and bisoprololo and a positive family history of Type 2 diabetes. At admission, she was dehydrated and lethargic, but can be awakened after painful and verbal stimulation, and motor strength was quite. Plasma glucose concentration was >600 mg/dL with mild metabolic acidosis at blood gas and Na values were 150 mmol/L. IA2 and GAD auto-antibodies measurements were negative. Insulin, c-peptide and HbA1c levels were significantly high. Effective serum osmolality >320 mOsm/kg. Rehydration was started with isotonic saline (0.9% NaCl) infusion and thereafter continued with 0.45% NaCl. In addition, continuous insulin administration at 0,012 UI/kg/h was introduced with the dosage titrated thereafter to achieve a decrease in serum glucose concentration of 50-75 mg/dL/h. Basal-bolus insulin administration was started during the third day of admittance.

Hyperosmolar hyperglycemic syndrome (HHS) is a clinical state characterized by hyperglycemia (blood glucose 33 mmol/L or 600 mg/dL), hyperosmolarity (serum osmolality 320 mmol/kg), and minimal ketonemia, is often described in adults with established diabetes, but rarely described in pediatric age especially in the prepubertal phase. Additionally, almost 28% of pediatric patients with HHS can also present with concomitant diabetic ketoacidosis (DKA). Due to the high mortality rate and severe complications associated with HHS, it is imperative to distinguish between DKA and HHS as the initial management can highly influence clinical outcomes.

Although HHS represent a relatively common condition in adult obese subjects with T2D at onset, the rising prevalence of severe obese and type 2 diabetes in children might be associated in the next future to a parallel increase of its diagnosis in childhood. Therefore new cases and especially pediatric guidelines for most appropriate treatment of this condition are needed.

P3-315

Associations between pituitary abnormalities and treatment response in children with growth hormone deficiency. First multicenter study in Portugal

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Background/Aims: Magnetic resonance imaging (MRI) is used to investigate the etiology of growth hormone deficiency (GHD). There is a close relationship between structural changes in the pituitary gland and clinical status.

We aimed to investigate the relationship between MRI findings and clinical symptoms and treatment response in children with GHD.

Methods: The study was conducted in nine Department of Pediatric Endocrinology of Portugal. The study group included GHD children treated for at least two years whose magnetic resonance imaging was available. Patients whom were small for gestational age, with clinical syndromes, chronic diseases or acquired GHD were excluded. Clinical presentation, hormonal status and first year growth response were compared between patients with pituitary abnormalities and patients with normal MRI. Results are presented as mean± standard deviation score (SDS) unless stated otherwise.

Results: Three hundred and twenty-one children were included, of which 230 were male (67,6%). The mean age at the start of treatment was 9,68 ± 4 years. Additional hormone deficiencies were found in 44 (13%) of patients. Pituitary MRI showed alterations in 141 (43,9%) patients; several patients showed more than one abnormality: 100 had pituitary hypoplasia, 71 had thin stalk, 58 had ectopic posterior pituitary, 16 had empty sella and 31 had the triad ectopic posterior pituitary, pituitary hypoplasia/aplasia and stalk defects. Patients with pituitary abnormalities started treatment significantly earlier ($8,5 \pm 1,2$ years vs $10,61 \pm 3,7$ years; $p=0,000$) and they had a more severe clinical phenotype (height SDS $-3,26 \pm 1,2$ vs $-2,89 \pm 0,84$; $p=0,001$) than patients with normal MRI. A statistically significant increase was observed in the variation of height increase rate after one year of treatment between the two groups ($0,91 \pm 1,04$ vs $0,59 \pm 0,57$; $p=0,001$).

Conclusions: MRI is a useful tool in assessing GHD patients. The presence and type of hypothalamic-pituitary abnormalities provides valuable information regarding the likely severity of the GHD and predicting treatment response.

P3-316**Epidemiological and socioeconomic changes in the child population from debut DM1 in this 21st century**

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Objectives: To demographic, socio-economic and social changes in the population of children who debuted in this century with DM type 1a.

Patients And Methods: Study patients with Type 1 Diabetes Mellitus from January 2000 to the present. Longitudinal study of global epidemiological, social, demographic and clinical variables and by five-year periods, focusing on the latte at Basque Country.

Results: 105 patients (34% M / 66% H), with age at diagnosis of 8.7 ± 3.1 years (43% with ketoacidosis vs 57% without ketoacidosis), HbA1c average to debut of 10.9 +The incidence declared in Euskadi is 12.9 cases / 10 5 57% are families of Spanish origin, 43% at least one parent is a foreigner. If we value the last five-year period, the proportions are 28% foreign vs. 72% foreign. The rate of foreigners <15 years in Euskadi is 8.2%, Alava 16.8%. The OR of children with DM type 1 debut is 2.55 globally (p: 0.001) and in the last five years of 4.20 (p: 0.0001). If we value this sub-population, the degree of CAD is 70% (OR 2.5 p.001 vs foreign), HbA1c average of 11.5%, a duration of symptoms of 4.8 weeks (OR 2.5 p.001 versus outsiders), 100% autoimmunity, 15% other autoimmunity. 16% of families at debut had a "non-classical" family unit (separation, divorce, single parents). Similar to average family data with children in Euskadi 18%. At the end of the study and after several years of debut (average 5.8 years) the rate was increased to 28%. OR 1.80. If we study the sub-group of foreign population (43 families, 2 at debut (5% p: 0.01 with respect to outsiders)) they were in this situation. After the study, this subgroup had not modified the rate.

Conclusions: We assume that this study may have some deficiencies due to the regionalization of the sample, but demonstrates a real social change in our population with an impact on diabetic pathology. There is a more vulnerable population (by genetics, culture, customs), which in turn is increasingly numerous: the immigrant; who comes later to consult Debuts e most prevalent clinical situation worse (CAD). The barriers and language and cultural differences are added handicap in monitoring these patients. On the other hand, the debut of a child can be a cause of serious family breakdown, as evidenced by the increase in the separation rate. This makes us suggest recommending an increase in emotional support for these families.

P3-317**Body Mass Index and Incident Type 1 Diabetes in Children from Lesser Poland over an 11 year observation period**

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Background: One of the speculated causes of the decreasing age of onset of type 1 diabetes is the increase in body weight in children. This so-called *accelerator hypothesis* is, however, controversial. The aim of the study was to test whether younger age of type 1 diabetes onset is associated with higher BMI-SDS at the time of diagnosis.

Methods: Retrospective data analysis from medical records of all patients under the age of 14 (n=559; 50.6% male), with newly diagnosed type 1 diabetes in Lesser Poland between 2006 and 2017.

Results: There were only 15 (2.7%) cases of obesity at the moment of diagnosis. An increase in BMI-SDS by 1 unit was associated with the development of the disease 0.54 years later. Interestingly, BMI-SDS was higher in the older age groups, during puberty.

Conclusion: The results of the present study do not confirm that younger age of type 1 diabetes onset is associated with higher BMI-SDS at the time of diagnosis, and therefore are insufficient to prove the *accelerator hypothesis*. However, the results point to a possible contribution of increased body weight during puberty on the age of type 1 diabetes manifestation. This concept requires further investigation.

P3-318**Novel mutation in HNF4-alpha gene and reclassification of diabetes in a family**

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11-year-old female, admitted in the emergency room due to postprandial hyperglycemia (350 mg/dL) in her father's glucometer without ketosis or acidosis. She referred one-month evolution of mild symptoms, as polydipsia, polyuria, sporadic abdominal pain and nocturia.

She was the first child of non-consanguineous parents, born full term at vaginal delivery with a birth weight of 3760g (90th percentile). Since 5-years-old her weight was between 85th-97th percentiles (classification: overweight). There was family history of diabetes. 43-year-old father was diagnosed with type 2 diabetes

(T2D) since he was 10-years-old (detected in routine laboratory tests but without symptoms). Initially he was treated with oral antidiabetic drugs (metformin and glibenclamide). He started insulin therapy at 23-years-old due to persistent hyperglycemia with high glucose values (600 mg/dL) and symptoms like polydipsia and polyuria. He was never overweight and actually he has diabetic retinopathy. 73-year-old paternal grandmother was diagnosed with T2D at 50-years-old and she is currently under insulin therapy. The remaining family history is irrelevant.

Analytically: there was no ketosis (ketonemia 0.1); no acidosis in venous gasometry; normal complete blood count; normal values of albumin, magnesium, phosphate, potassium, sodium, chloro, and calcium; normal values of triglycerides, total cholesterol, high-density lipoprotein and low-density lipoprotein; negative celiac disease screening; HbA1c 12.0%; normal thyroid function and negative antibodies; insulin 28.5 (reference value: 6-27 uUI/mL) and C-peptide 2.22 (reference value: 0.8-6.0 ng/mL).

Auto-immunity study was negative for glutamate decarboxylase autoantibodies, insulin autoantibodies, zinc transporter autoantibodies, islet of Langerhans autoantibodies and HLA DQ2-DQ8. A genetic study was requested on suspicion of Monogenic Diabetes (MODY): the variant c.602A>Cp (His201Pro) in the HNF4-alpha gene was found in heterozygosity. Subsequently, a genetic study was also performed on the father, and the same variant was found.

Currently, 9 months later, she is under metformin 500 mg twice a day, and multiple daily insulin injections therapy with requirements of 0.6 U/kg/day and HbA1c 8.1%.

The authors decided to present this case since this genetic variant is not described in the literature. The diagnosis of this adolescent also allowed the reclassification of the father's diagnosis of diabetes. A correct classification of diabetes is important because it can predict the clinical course of the disease, clinical orientation and pharmacological treatment.

P3-319

Systemic lupus erythematosus, Celiac and Hypothyroidism complicating type 1 diabetes: a rare tetrad

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The association of TIDM and SLE is rather rare, but in the event of occurrence can complicate the course of the other. Genetic predisposition, autoimmunity and viral infections are the main etiopathological factors implicated in the pathogenesis of type 1 diabetes mellitus and an association between TIDM and Celiac disease (CD) has a high incidence. This is probably due the human leukocyte antigen (HLA) DR3- DQ2 and DR4-DQ8 that is common to both the diseases.

A 9 year-old girl, was diagnosed with TIDM with Hba1c of 9.3, she was started on Insulin degludec and glulisine and was maintaining normal sugars. Her IgA anti-tissue transglutaminase antibodies (AtTG) was positive – 101 RU/ML, which was followed up with a duodenal biopsy showing villus atrophy and increased intra-epithelial cells, confirming the diagnosis of CD and was

advised a gluten free diet. Her anti thyroid peroxidase (TPO) was > 573 IU/ml (positive) but her TSH and Free T4 were within normal limits and hence were regularly followed for her thyroid functions regularly.

After three years, she developed high-grade fever and macular rashes on her face, palms and sole. Her blood and urine cultures were sterile. Anti-nuclear antibodies (ANA) and anti double stranded DNA (ds DNA) sent for evaluation of fever, were strongly positive. The thyroid function tests, anti TPO and anti thyroglobulin were repeated and were strongly positive with low free T4 and high TSH, she was started on tab thyroxine 25ug once a day.

The child came back a month later with facial swelling, with a diagnosis of SLE, 24 hour urinary protein and urine protein creatinine ratio was sent. Her blood pressure was 100/60 mm of Hg. The results were very high (in table), following which a kidney biopsy was planned. The biopsy reported focal proliferative lupus nephritis class III (ISN/RPS classification 2004). She was given intravenous methyl prednisolone pulse for three days and then started on oral mycophenolate and oral corticosteroids.

Genetically predisposed patients are known to have associated autoimmune conditions manifesting together. Although reports say 30% of patients with SLE may develop two or more autoimmune disorders, type 1 diabetes mellitus is a very rare association.

There needs to be an awareness that 2 or more auto immune conditions can exist in the same patient or even develop progressively. This would be the first case to report the tetrad of TIDM, CD, autoimmune hypothyroidism and SLE in the same child.

P3-320

EpiPEG-PreMeb study: chemerina plasmatic and metabolic syndrome relation at SGA childrens

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The objective of this study has been the analysis of plasma chemistry in a group of children born SGA at the University Hospital of Álava-Txagorritxu and biochemical parameters related to the metabolic syndrome.

Material and methods: In a cohort of 27 subjects sub (13 boys and 14 girls) from the epiPEG-PreMeb study, a blood sample at 3, 12 and 24 months of life it was extracted. Biochemical parameters s and measured by automated and chemistry levels by ELISA kit (Chemerin human ELISA, Biavendor). The PEG condition was established when the subjects presented a weight or length of at least 2 standard deviations (SD) below, taking as reference the Spanish growth curves (Carrascosa et al., 2010). For stratifying kind of catch-up, the evolution of weight gain / height for the measurement s was compared: catch-up len t o Δ <0.49 DE, normal Δ 0.5-1 DE and fast Δ > 1 DE. Statistical analysis included the Pearson correlation coefficient or Spearman 's rho, and the distribution of the data was determined by the test of Shapiro - Wilk (SPSS Statistics v24).

Results and conclusion: Positive correlation was observed between the concentrations of chemerine at 3 months as glucose, triglycerides (TG), insulin, as well as HOMA, and TG and C - reactive protein (CRP) after 24 months. Stratifying by sex, in children positive correlations were found between the chemistry and TG at 3 months and with CRP at 24 months. In girls, the correlation was given with glucose, TG and HOMA at 3 months and with total cholesterol and LDL at 24 months. Regarding the type of catch-up, subjects with slow catch-up presented positive correlation between chemistry at 3 months and TG, insulin and HOMA at that same age. In who they submitted catch-up normal positive correlation was observed between Concentration of chemistry at 3 months and glycemia at three months and TG concentrations at 24 months. Therefore, by this means, we can conclude that chemistry levels measured at an early age in PEG children could be considered an indicator of future alterations of biochemical parameters related to the metabolic syndrome, especially in cases of slow catch-up.

P3-321

Hydrometrocolpos due to congenital adrenal hyperplasia – A rare cause of bladder outflow tract obstruction in a female child

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Introduction: Hydrometrocolpos (HMC) develops in a female child as a result of a vaginal outflow tract obstruction and accumulation of secretions. HMC can have associated with other malformations or associated syndromes. Imperforated hymen, vaginal atresia, persistent urogenital sinus, and cloacal malformation, are the common causes for HMC. Congenital adrenal hyperplasia causing androgen exposure during the fetal life leads to varying degree of ambiguous genitalia. Androgen exposure before 12 weeks of gestation leads to, labial fusion and persistent urogenital sinus (PUGS). Accumulation of bladder and vaginal contents in the common channel leads to pressure effect which can leads to bladder outflow obstruction (BOO) and varying degree of hydronephrosis.

Case report: A term infant presented with abdominal distension, bilateral ballotable masses and clitoromegaly. No palpable gonads were identified in the labioscrotal folds or in the perineum. She had urethral opening without separate vaginal orifice. Anal opening in the normal position. Ultra sound (US) abdomen and pelvis revealed distended bladder, bilateral severe hydronephrosis. Right side ovary was identified and it was normal in size. There was a well define cystic area, posterior to the bladder suggestive of hydrometrocolpos possibly due to PUGS. BOO and bilateral severe hydronephrosis caused hypertension, which needed vesicostomy. After decompression of BOO follow up US showed normal kidneys without hydronephrosis. Karyotyping reveled 46,XX and the baby had elevated 17 hydroxy progesterone, which confirmed the diagnosis of congenital adrenal hyperplasia. She was started on hydrocortisone and fludrocortisone and arranged micturating cystourethrogram to confirm the diagnosis. She is awaiting definitive surgical correction of PUGS.

Conclusion: This case highlights the varying degree of urogenital abnormality caused in CAH. Multidisciplinary care is needed for patients with androgenital syndrome in CAH.

P3-322

Bartter syndrome complicated with growth hormone deficiency due to a suprasellar arachnoid cyst

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Introduction: Bartter syndrome (BS) is a rare genetic renal tubular disorder characterized by hypokalemia, salt-wasting and metabolic alkalosis. Polyuria, polydipsia, hypokalemia and salt loss are responsible for the growth retardation seen in BS. Persistent growth failure despite optimizing medical therapy may be due to growth hormone (GH) deficiency.

Case diagnosis and treatment: A 9-year-old girl diagnosed with Bartter syndrome was referred for evaluation of severe short stature (92.5 cm, -7.7 standard deviation). Classical BS was diagnosed when she presented with typical clinical manifestations and characteristic biochemical abnormalities at 4 months of age. Her medical therapy consisted of indomethacin, salt and potassium supplements. Her bone age was markedly delayed and glucagon-stimulated growth hormone level showed a peak of 2.9 ng/dL. Thyroid hormone and cortisol levels were normal. Magnetic resonance imaging showed a dilated suprasellar cistern communicating with dilated 3rd ventricles, with no contrast enhancement elucidated; suggestive of a suprasellar arachnoid cyst. The dilated structures minimally compressed the pituitary gland. She showed excellent response to recombinant growth hormone therapy. The absence of obstructive symptoms did not warrant an immediate neurosurgical intervention.

Conclusions: The case indicates a possible association of suprasellar arachnoid cyst in BS not previously reported. Furthermore, the importance of evaluating for GH deficiency in children with persistent growth retardation to conventional therapies of BS is highlighted.

P3-323

De Novo PPM1D Mutation in a Patient with Growth Hormone Deficiency: A case report

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Growth hormone deficiency (GHD) is a relatively rare cause for short stature resulting from insufficient secretion of growth hormone (GH). With complicated etiology, GHD can coexist in numerous syndromes or disorders such as Turner Syndrome. So, it is necessary to take genetic analysis to patients with GHD

especially those perform various phenotypes. A 9.5 years old boy complained of short stature was diagnosed with GHD by height velocity (HV) <5 cm/year, delayed bone age and GH peak concentration of <5.0 ng/mL in two different stimulation tests with no abnormal magnetic resonance imaging of pituitary. The boy also had feeding difficulties and behavior problems. Further test of Wechsler Intelligence Scales showed mild intellectual disability. Without other dysfunction, we suggested his family to perform trios whole exome sequencing (WES) to identify genetic cause and the results revealed a novel mutation of PPM1D(c.1434C>A). PPM1D was reported in two meta-analysis as a new gene leading to intellectual disability (ID). And it was described as a cause for ID in 14 patients in 2017, apart from ID, the phenotypes included high pain threshold, behavioral problems, periods of fever and vomiting, short stature and so on. Another case report also presented an individual with mutation of PPM1D in 2018 who also had short stature but no gastrointestinal difficulties or fever. Assay of GH was not reported in these papers, that GH assay might be needed more attention.

P3-324

Hypoglycemia in a patient with Turner syndrome and Kabuki make-up

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The patient was a Chinese girl who born 40 weeks of gestation by caesarean section. Her birth weight was 2900g (10th–25th centile), birth length was 48cm (10th– 25th centile). Both parents are in good health. The family history was unremarkable. She was first admitted to our hospital because of seizure afebrile at 6 months old. She presented discontinues generalized tonic-clonic seizures for 3~5minutes several times, it seemed that these onsets were not associated with fever or any sign of infection. She was found extremely hypoglycemia with a blood glucose concentration of 1.8mmol/l(range 3.3–5.5mmol/l) . Her length was 67cm (<p3< span="">), weight was 6.7kg (<p3< span="">), head circumference was 43cm. BMI was 14.92kg/m², blood pressure: 80/50mmHg. She had special facial features reminiscent of the Kabuki syndrome, eversion of the lower lateral eyelid, arched eyebrows with the lateral one-third dispersed, a depressed nasal tip, and prominent ears. She showed widely spaced nipples and cubitus valgus. </p3></p3>

Laboratory examination: ALT 34u/l (0-40); AST 48u/l (0-40); Creatine 48umol/l(32.3-54.2), Electrolytes : normal. Blood gas analysis: PH 7.44, PCO₂ 29.6mmHg, HCO₃ 22.4mmol/L, BE -0.6mmol/L. Results of the hormones at the time of hypoglycemia (fasting test , plasma glucose 1.8(mmol/L)) as follows: Free fatty acids 0.3 (mmol/L); urine ketone bodies: Negative; plasma lactate 1.8(mmol/L)(normal<2); Serum ammonia 52.2(μmol/L) (normal<80) ; serum insulin levels 2.9 mU/L, serum cortisol 281mmol/L, adrenocorticotrophic hormone 202pg/mL; serum growth hormone 5.5ng/ml; serum free thyroxine 12ug/dl (normal 10.8-20); HbA1C4.2%(normal 4-6); luteinizing hormone 7.92IU/L; follicle-stimulate hormone 93.64IU/L; estrogen<18.35pg/ml. Electroencephalogram (EEG) result did not show any abnormalities.

Brain MRI: no abnormalities. Pituitary stalk integrity. Echocardiography: show no evidence of congenital heart disease. Her 72-hr blood glucose profile was abnormal (lowest 2.1mmol/L; highest 5.9mmol/L; time of duration <2.9mmol/L:5hours) Her hypoglycemic screen showed inappropriately raised, given these biochemical features she was diagnosed with hyperinsulinemic hypoglycemia.

No typical mutations in the genes ABCC8, GLUD1, KCNJ11, GCK which are associated with hypoglycemia, were identified by NGS. Cytogenetic analysis revealed 2 cell lines: 50% showed a single normal X chromosome and a marker chromosome, mos46, X, +mar ;50% had just a single normal X chromosome.

She was given the diagnosis of Turner syndrome, clinical manifestations reminiscent of Kabuki syndrome was because of KDM6A mutation.

P3-325

45X/47XXX Mosaicism and progressive puberty

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Objective: To report a case girl with 45X/47XXX mosaic Turner syndrome exhibiting a progressive puberty.

Design: Case report

Result: A 9 years 4 months old girl was presented with growth retardation. Chromosome analysis revealed a mosaic karyotype 45X/47XXX. She presented with normal height but much lower than the mid-parental height. During annual check-ups, her growth rate was accelerated without growth hormone treatment, her physical examination revealed a Tanner stage II to stage IV and menarche occurred spontaneously in 14 months.

Conclusion: A few rare cases of progress puberty with mosaic Turner syndrome have been described. Here we describe a case of TS with the 45X/47XXX presenting with growth retardation, onset of spontaneous progressive puberty. Although the mechanism leading to progressive puberty in this condition is still unknown, the present report discusses this rare presentation and gives an overview on the current literature regarding this case.

Keywords: Turner syndrome, progressive puberty, 45X/47XXX mosaicism

P3-326

Vitamin D and Type 1 Diabetes Mellitus in Children

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Backgrounds: The understanding of the efects and role of vitamin D and its analogues in the functioning of body tissues, systems and organs has improved substantially over the last decade. The potential extra-skeletal role of vitamin D has been a rich area of interest and research over the last decade. Vitamin D deficiency has been implicated in a variety of chronic diseases, including

bone mineral disease, autoimmunity, cancer, and diabetes. Many epidemiological studies have found high prevalence of vitamin D deficiency in children with type 1 diabetes mellitus, suggesting a strong relationship between the two.

Objective: Aims of this study were to measure 25 hydroxy vitamin D (25 OHD) level in type 1 diabetes mellitus and to compare them with 25 hydroxy vitamin D (25 OHD) levels in non-diabetic subjects at the same period.

Methods: A cross sectional study was carried out between 2018 - 2019. This study including 40 patients with type 1 diabetes mellitus at Saiful Anwar Hospital, Malang, Jawa Timur and 40 children non-diabetic control children. Clinical data 25OHD serum level were collected and measured with Enzyme-linked Immuno Assay (ELISA) method. A serum plasma 25(OH)D concentration of <20 ng/ml was considered as deficiency, a concentration between 21 and 29 ng/ml as insufficiency, and a plasma concentration above 30 ng/ml as normal (sufficient).

Results: The mean serum 25OHD in type 1 diabetes mellitus children was 20.35 ± 5.28 ng/ml (range 1.07 – 26.64 ng/ml) and in the controls was 29.46 ± 4.07 ng/ml (range 2.86 – 33.3 ng/ml). The mean serum 25OHD in type 1 diabetes mellitus children was lower than that of controls ($P = 0.69$).

Conclusion: Children with T1DM have lower vitamin D levels than control group.

Keywords: Vitamin D, type 1 diabetes mellitus, children and adolescents.

P3-327

Severe hypercalcaemia after years on the ketogenic diet: A novel case report

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Introduction: An association between the ketogenic diet (KD) and hypercalcaemia has been suggested in one case series of three children¹, where hypercalcaemia occurred within 12 months of starting KD. We describe a case where severe hypercalcaemia occurs after four years on KD.

Case: A 5.5-year-old boy is referred for hypercalcaemia in context of early sepsis and a background of Dynamin-1 gene mutation causing infantile epileptic encephalopathy and developmental delay. He had been commenced on KD at 18 months of age due to drug-resistant seizures. A Deep Brain Stimulator (DBS) was inserted at three years for refractory hyperkinetic movements. He has since been on intermittent long-term antibiotics for recurrent DBS infections without systemic symptoms.

There were no recent changes to his medications: sodium valproate, gabapentin, clobazam, clonidine, and intravenous flucloxacillin and azithromycin.

Table 1. Investigations on presentation.

Investigation	Result	Reference Range
Corrected calcium	4.07 (High)	2.19-2.69mmol/L
Phosphate	1.7	1.0-1.9mmol/L
Alkaline phosphatase (ALP)	99 (Low)	139-347IU/L
Parathyroid hormone (PTH)	6 (Low)	10-65ng/L
Magnesium	0.9	0.65-1.05mmol/L
Creatinine	73 (High)	24-45umol/L
Vitamin D	84	>50nmol/L
PTH-related protein	<1.40	<1.40pmol/L
Urine Calcium:Creatinine Ratio	1.3 (High)	0.05-0.60
Vitamin B6	70.1	35.2-110.1nmol/L
1,25 Vitamin D	24 (Low)	48-192pmol/L
Chest/hand/wrist Xrays	Low bone mineral density, otherwise normal	
Renal Ultrasound	Nephrocalcinosis	
Full Blood Count		
Thyroid Function Tests	Normal	
Electrolytes		
DEXA scan		

Calcium was normal six months prior to presentation (2.57mmol/L), but intermittent mild hypercalcaemia was noted over the last 12 months (highest 2.83mmol/L). ALP had been low over the past three years.

Hypercalcaemia persisted despite hyperhydration and two pamidronate infusions. He subsequently became unstable due to DBS infection and was managed with surgical intervention and antibiotics. Calcium normalised after two weeks of hyperhydration, but increased after cessation of hyperhydration.

KD was gradually weaned and replaced with low calcium milk. Once KD was ceased, serum calcium normalized and remained normal after hyperhydration was discontinued. Calcium remained stable and PTH increased after one week to 73ng/L. Calcium was gradually re-introduced into his diet to 500mg/day with no recurrence of hypercalcaemia and normalization of PTH.

Conclusion: This case suggests that severe hypercalcaemia may occur several years after commencement of KD and can be refractory to standard management. In this case, the hypercalcaemia may have been caused by the combination of long-term KD and sepsis with acute kidney injury. However, despite resolution of sepsis and acute kidney injury, his hypercalcaemia did not fully resolve until KD was ceased.

P3-328

Estrogen Production by Sertoli Cell Tumor in Unusual Case of Testicular Feminization Syndrome

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A 5-year-old patient was brought by her parents to our pediatric endocrinology Outpatient clinic with history of progressive bilateral breast budding and enlargement since 3 months ago. Her previous medical history were uneventful; there was no family history of precocious puberty. Parents were married, nonconsanguineous, she has 1 other sibling who is well. At presentation, our patient was a well looking girl, She had a full female phenotype: On initial physical examination the breasts were abnormally developed compatible with Tanner stage III. The gynecological exam reveals normal external female genitalia, the vagina and hymen were seen, but Pubic hair was not. Clinically her weight was 24 kg (90 percentiles on CDC growth charts), her height was 124 cm (95th percentile on CDC growth charts), there was no advanced bone age in X Ray.

Excepting elevated estrogen levels other hematological and biochemical profiles including thyroid function test were normal. The levels of gonadotropins were measured and found (FSH 3.18 mIU/mL, LH 0.8 mIU/mL), estradiol was 64 pg/ml. but initial ultrasonographic study of abdomen and pelvic ultrasonography showed no abnormality, brain MRI was also normal. After getting all this investigation, we came to conclusion the patient may be suffered from constitutional prepubescent puberty.

Despite this She was regularly monitored, after 3 months her breasts began to grow rapidly became as large as tanner stage of IV and she had 4 cm increasing in her height. Repeat of hormonal assay showed high levels of estradiol, 145pg/ml but tumor markers

levels were normal, with a total BHCG of 0.1mlU/ml and an alpha-fetoprotein of 0.9IU/ml. At this time second thorough abdominal and pelvic ultrasonography workup revealed a round solid hypo echo and vascular structure mass measuring about 26.23mm in her left pelvic cavity. Surprisingly The pelvic MRI also detected, the lack of uterus and ovaries and short blind- end vagina, with oval shape structure measuring about 10 .6mm right side of pelvic cavity. For this reason The blood sample was sent to the molecular karyotyping laboratory for detection of chromosomal abnormality. This test confirmed the suspected diagnosis of - testicular feminization syndrome 46XY.

P3-329

Dysphagia and dyspnea by lingual thyroid mass in a young child: what to do?

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Background: Ectopic thyroid tissue can be found anywhere along the normal path of thyroid descent, but is most commonly found at the base of the tongue, in which case it may be referred to as a lingual thyroid. Although the patients are usually asymptomatic, it can lead to symptoms such as dysphonia and dysphagia. We present a child patient with a lingual thyroid resulting in severe dysphagia that was cured surgically.

Case presentation: A 4-year-old male child presented to our department for failure to thrive estimate at less 2 DS. He Present a severe dysphagia to food, some episodes of transitional dyspnea, hypothyroidism treated since 1 year with lévothyrox. Examination of the neck revealed no palpable thyroid gland in the normal pré-trachéale position, no cervical adenopathy and normal oral cavity.

Thyroid hormone tests showed elevated TSH, TG (thyroglobulin) concentrations and decreased FT3, FT4 concentrations. The ultrasound exam shows an oval mass lobed echogenic and homogeneous measuring 1.4 x 1.0 cm without discernable isthmus. The thyroid scintigraphy with 99mTc-Pertechnetate showed an uptake region at the base of the tongue representing a lingual thyroid. There was no thyroid uptake in the usual site in the neck. CT image showing intensely enhancing mass in the base of tongue and absent native thyroid issue in the thyroid bed.

Increased dose L-thyroxine was started and surgery because sever dysphagia was performed. The patient made a good post-operative recovery and the clinically symptoms decreased.

Conclusion: An ectopic thyroid should be considered in any child with presence of hypothyroidism and surgical indication is to be expected after exploring all dyspnea and /or dysphagia.

Keywords: lingual thyroid, hypothyroidism, child, dysphagia, surgical indication.

P3-330

Van-Wyk Grumbach syndrome associated with trisomy 21: a case report

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Algeria

Introduction: Van-Wyk Grumbach syndrome (VWGS) described in 1960 associate Primary hypothyroidism to early puberty, polycystic ovaries and pituitary adenoma with or without hyperprolactinemia. It is a very rare cause of precocious puberty, which the etiopathogenesis is not yet very clear.

Observation: We report the case of an 8 year old girl known for trisomy 21, she presented a Primary hypothyroidism treated initially with Levothyroxine at low dose and developed 6 months later an early puberty with vaginal bleeding and polycystic ovaries suggesting the diagnosis of VWGS. Her MRI showed a pituitary macroadenoma that resolved completely after only 90 days of adequate dose of levothyroxine with clinical and emotional improvement.

Conclusion: The Van-Wyk Grumbach syndrome is very rare, but remains an important entity to know because of its good prognosis under medical treatment that avoids the use of unnecessary surgeries (polycystic ovaries) and risky (pituitary macroadenoma).

P3-331

Fahr syndrome in young boy with hypoparathyroidism

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Background: Fahr syndrome is a rare degenerative disease, characterized by the presence of calcification of the basal ganglia. Autosomal recessive or dominant, variable penetrance.

Usually asymptomatic in the first 2 decades, the disease typically manifests itself either at 30 years of age by the appearance of neuropsychiatric disorders, or at age 60 by progressive dementia with extrapyramidal syndrome.

Case presentation: we report the case of a 9-year-old child left with a history of generalized epileptic seizure disorder under treatment then the 45th day of life, orient for hypocalcemia associate with a Fahr syndrome discovered as a result of walking disorder with claudication of the lower limb, the clinical examination finds a child with mental retardation without statural delay, dental hypoplasia, signs of hypocalcemia: paresthesia, cramp, Chvostek's sign and Troussseau's signs present. Neurological examination showed an aphasic child with extrapyramidal syndrome.

The biological examinations showed significant hypocalcemia and hyperphosphatemia. The serum parathyroid hormone level was very low. Cerebral computed tomography revealed bilateral calcifications of the basal ganglia.

The diagnosis of hypoparathyroidism caused Fahr syndrome was retained. Initiated treatment included calcium 2 g/d and vitamin D3 (one alpha).

Conclusion: our observation underlines the value of investigating in children the existence of abnormalities of the phosphocalcic metabolism with Pth assay in subjects carrying cerebral calcifications, and particularly in patients with Fahr syndrome.

P3-332

Thyroid cancer in a child with graves's disease

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The association of thyroid carcinoma with Graves' disease is considered rare and remains exceptional because it accounts for only 1-2% of childhood cancers.

We report an observation of a 10-year-old girl from a goitrous endemic area (CHLEF) with exophthalmia. It shows signs of obvious thyrotoxicosis with a very firm, homogeneous and asymmetrical goiter on the right. A hormonal assessment, an echography and a thyroid scintigraphy confirm the diagnosis of Graves' disease. The patient is treated with ATS for 4 years and then operated on by total thyroidectomy. The patient was then placed on levothyrox and a follow-up ultrasound as well as the operative and anapathological report were requested.

Ultrasound refers to an empty thyroid compartment and no ADP or thyroid abnormality. The anatomo-pathological study shows a well-differentiated vesicular carcinoma of the thyroid and the surgical protocol reports only the concept of total thyroidectomy without lymph node dissection. We decide to do an irotherapy and then to prescribe to the patient a frenator treatment based on levothyrox. The follow-up is ensured at our level since already 5 years without any other complication.

Our observation reinforces the literature series on the frequency of the association of Graves' disease and thyroid carcinoma in children and stresses the message that hyperthyroidism is not a guarantee against thyroid cancer.

Keywords: Graves' disease - Thyroid carcinoma- Child.

Influence of nocturnal hypoglycemia on school performance of teens with DM type1

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It is known that a larger number of blood glucose control, glycemic control of patients with type 1 Dm suffers improvement. Likewise, the presence of hypoglycaemias maintained, especially at night and in school-age patients, could have a significant influence on neurological aspects such as night rest, learning and memory. Improved technology has id allowed or development of control devices interstitial glucose, both blinded (retrospective) as erta abi (real time). The free FREE STYLE device is one of the most widely used in our environment because it is in the Services Portfolio since the end of 2017.

Objective: To assess the impact of nocturnal hypoglycaemias on the final school performance of adolescents affected by type 1a DM by studying the periods of hypoglycemia recorded through the use of FREESTYLE.

Methods: DM1 children over 12 years in secondary school, with at least 6 months duration from the debut. Use of free FREESTYLE system>85% of the study period. Prospective longitudinal follow-up. Rating or f time hypoglycemia (blood glucose <70 mg / dl) from March to June 2018; analiz ando schedule period 8:00 p.m. to 8:00 am; and the average scores reached at the end of the course (1-10) in core subjects (language, mathematics, environmental knowledge, social, English) Comparative study .IBM SPSS Stastistics 19.0., Paired nonparametric samples n <30. Survey of Health Questionnaire SF-36 (Spanish and summary).

Results: 25 children (17♂), 1 course repeater, average age 14.5 to [12-17.5]. Needs: 1.1 IU / kg / day [0.88-1.56], sensitivity 58 mgr / dl / IU [25-102] H bA1c (DCA): 7.7% [6.8-9.2] p: 0.38, Events of hypoglycemia / month 4, 9 [3-8] Hyperglycaemia events / month 8 [7-20]. Night study hours 38% hyper (> 180 mgr / dl) in normo 44% (70-180 mgr / dl and 18% in hiccups (<70 mgr / dl) Average grade study 7.25 If you select those patients who spend on average> 33% of the night shift in hypoglycemia, they are 8/25 cases The distribution denotes average for this group of 6.6 vs 8.1 p: 0.02 95% IC.

Author Index

Numbers refer to abstract numbers

A

- Aarts, Coranne P1-92
Abaci, Ayhan P3-198, P3-250
Abaci, Ayhan P1-285
Abaci, Ayhan P1-28, P2-284
Abali, Saygin P1-159, P1-175, P1-273
Abali, Zehra P1-10
Abali, Zehra Yavas P1-134
Abawi, Ozair P1-196, P1-46, P1-47
Abbo, Olivier P1-132
Abd El Fattah, Magdy P2-33
Abd El-Gwad, Ahmed P3-77
Abd El-Latif, Soha P2-258
Abdalla, Maisa P1-320
Abdalrahman, Naiemh FC2.5
Abdel Meguid Ahmed, Shaymaa
Elsayed P2-50
Abdel Rahman Ismail, Eman RFC1.6
Abdel Wahab, Amina P3-94
Abdelghaffar, Shereen P1-141, P1-320
Abdelhedi, Fatma P1-94
Abdellaoui, Ouahiba P3-147, P3-147,
P3-148
Abdellaoui, wahiba P3-142
Abdelmaguid, Nadra P3-152
Abdelmeguid, Yasmine P2-265, P3-18
Abdulhadi-Atwan, Maha RFC3.3
Abdulla, Mohammad P3-185
Abdullah, Mohamed P3-290
Abdullatif, Mona RFC7.3
Abduvaliev, Anvar P1-325
Abe, Yuki P3-54, P3-63
Abe, Yuriko P1-333
Abedrabbo, Amal P1-188, P1-305, P2-203
Abid, Mohamed P1-94, P2-266, P2-39,
P3-170, P3-206, P3-216, P3-221,
P3-229, P3-25, P3-252, P3-97
Abo Elwafa, Reham FC4.5
Aboelenin, Hadil P3-77
Abokhashaba, Mohamed P2-33
Abozaid, Heba P3-73
Abraham, Mary P1-35
Abrigo, Enrica P1-300, P3-30
Abu Alrub, Shorouq p3-45
Abu-Libdeh, Abdulsalam FC11.3, P1-188,
P1-305, P2-203, P3-210, P3-298
Abu-Libdeh, Bassam P1-188, P1-305,
P2-203, P3-210
Abu-Libdeh, Bassam P3-298
Abulibdeh, Abdulsalam RFC3.3
Acar, Gulsen P2-51

- Acar, Sezer P2-12, P2-284, P3-124, P3-19,
P3-198, P3-2, P3-233, P3-250
Acar, Sezer P1-27, P1-285
Acerini, Carlo P1-10, P1-157, P1-167,
P1-262, RFC10.1
Acerini, Carlo L P1-6, RFC13.2
Achermann, John FC10.3, P2-2, S7.2
Acton, Dennis P1-52, P2-126
Adamova, Katerina LB-27
Adamsbaum, Catherine FC2.3
Adaway, Jo RFC13.2
Adel, Ashraf P3-165
Adel, Ashraf P3-160, P3-188
Adel, Djermane P1-292, P2-161
Adhami, Sara RFC7.1
Adler, Elodie P1-213
Admoni, Osnat P1-105, P1-430, P2-19,
P2-244
Aeppli, Tim P2-271, RFC10.5
Aerts, Isabelle P2-226
Afek, Arnon P2-123
Afhami, Shima P1-49
Afreh-Mensah, Donald P2-76
Aftab, Sommayya P2-143, RFC5.4,
RFC9.5
Agarwal, Neha P2-73, P3-227
Aghajanova, Elena FC14.4, P2-96, P3-289
Aghamahdi, Fatemeh P3-328
Aghayev, AghaRza P1-162
Aghayev, Agharza P1-134
Aghayeva, Asmar P2-5
Aguilar, Maria Isolina P3-157
Aguilera, Concepción P3-119
Aguilera, Concepción M P1-345
Aguilera, Concepción M. P1-33
Aguilera, Greti FC15.1
Agwu, Juliana C. P2-76
Agwu, Juliana Chizo P2-18, P2-210
Aharkov, Serhii P2-200, P3-110, P3-122
Ahmad, Ayesha P2-289
Ahmadov, Gunduz P3-87
Ahmed, Ahmed P3-94
Ahmed, Faisal P1-157
Ahmed, on behalf of the contributing
centres within the I-DSD registry and
I-CAH registry, Faisal RFC10.1
Ahmed, S Faisal P1-10, P1-126, P1-262,
RFC10.3, RFC13.2
Ahmed, S. Faisal FC2.5, P1-125, P1-167,
P1-6
Ahmed, S.Faisal P1-266, RFC3.1

- Ahmed, Saeed P3-310
Ahmed, Shayma P2-43
Ahmed, Syed Haris FC9.2
Ahmed, Syed Harris P1-113
Ahn, Moon-Bae P2-166, P2-85
Ahn, Moonbae P1-233, P2-122, P2-218,
P3-117
Ahn, Young-Min P3-88
Ai, Zhuanzhuan P1-191, P1-63
Ajlouni, Kamel RFC15.6
Akbal Isik, Eylul P1-117
Akbarzade, Azad P1-162
Akbaş, Emine Demet P2-99
Akcan, Nese P3-149, P3-266
Akcay, Teoman P1-162
Akduman, Filiz FC6.4
Akgun, Abdurrahman P1-283
Akgün, Bilçağ RFC6.4
Akillioglu, Kubra P1-117, P1-237
Akin, Leyla P2-169, P3-67
Akin, Leyla FC11.2
Akkus, Gamze RFC15.2, RFC8.5
Aksoylar, Serap P1-414
Aksu, Özden P1-48
Akulevich, Natalia P1-230, P3-191
Akurugu, Wisdom Alemya P1-1
Akyigit, Ali P1-71
Akin, Onur P2-137
Al Brahim, Nahla P2-67
Al Dubayee, Mohammed P1-161
Al Hamdan, Wejdan P1-161
Al Juraibah, Fahad P1-161
Al Kadaoui, Maria RFC1.4
Al Namshan, Mohammed P1-161
Al Qubasi, Mai P2-71, P2-98
Al Rifai, Hilal P2-71, P2-98
Al Saffar, Hussein P1-222
Al Shaikh, Hala P3-203
Al Yaarubi, Saif P1-222
Al-Yaarubi, Saif P1-11
Al-Ashwal, Abdullah P3-297
Al-Dubayee, Mohammed P2-31
Al-Enazi, Naser P1-266
Al-Gofi, Talal P3-297
Al-Juraibah, Fahad P2-31
Al-Khawaga, Sara P1-189
Al-Kindi, Adila P1-222
Al-Mansour, Salman P3-297
Al-Naim, Noora P3-28
Al-Naimi, Noora P1-381, P2-193
Al-Obaidly, Sawsan P2-71, P2-98

- Al-Olabi, Lara P2-112
 Al-Riyami, Nafila P3-20
 Al-Safi, Athba P2-193
 Al-Sagheir, Afaf P3-31
 Al-Shagrani, Mohammed P3-297
 Al-Shidhani, Azza P3-20
 Al_Thiabat, Hanan Farid Mufleh P1-251
 Alaaraj, Nada P2-156, P2-296, P2-43, P3-153, P3-160, P3-161
 Alaca, Raziye LB-6
 Alapetite, Claire P2-226
 Alarabi, Zohair P2-193
 Alavanda, Ceren P2-52
 Albanese, Assunta P1-98, RFC11.1
 Alberti, Luisella P1-423
 Albertini, Riccardo P1-428
 Albertsson Wikland, Kerstin P1-59, RFC12.6
 Albertsson-Wikland, Kerstin LB-9, P1-119, P1-250, P2-220, P2-229
 Albu, Alice P3-39
 Albuquerque, Edoarda V A RFC8.4
 Alcaide-Gantes, Alvaro P1-331, P2-118
 Aldalaan, Haneen P3-26
 Aldarsy, Nagwa P1-313
 Alderson, Julie P1-123, P2-253
 Aleem, Mahreen P1-288
 Alexander, Jacqui P3-155
 Alfakeeh, Khalid P1-161
 Alfano, Sara P1-409
 AlHerbi, Talal P1-161
 Alhinai, Shaima P3-76
 Alhubaishi, Zumaima P3-76
 Alhumaidy, Noora P3-165
 Ali, Salma P1-125, P1-167, P1-266, RFC3.1
 Alibrandi, Angela P1-300, P1-346, P1-422, P2-182, P3-164
 Alikasifoglu, Ayfer P1-239, P1-404, P2-223, P2-224, P2-59
 Alikor, Edward P3-311
 Alimova, Nasiba P1-325, P3-49
 Alimova, Nasiba Usmanovna P2-104
 Alimussina, Malika P1-126, RFC10.3
 Aliu, Nijas P1-281
 Aljaser, Fahed P3-183
 Alkan, Afra P1-162
 Alkan, Murat P1-411
 Alkhalifah, Reem P1-178
 Allegri, Anna Elsa Maria P1-251, P1-252, P1-391, RFC2.4
 Allen, Gabrielle P1-190
 Allende, Fidel P2-46
 Allgrove, Jeremy P2-36
 Almagor, Tal P1-430, P2-146, P2-244
 Almashanu, Shlomo P1-295, P1-430
 Almstrup, Kristian FC14.2, P1-399
 Alolga, Suzanne P1-371, RFC14.6
 Alonso Rubio, Pablo P1-272
 Alonso, José Antonio P2-239
 Alotaibi, Ahlam P1-178
 Alotaibi, Mohammed P2-15
 Alp Nalci, Kemal LB-2
 Alrawahi, Athila P3-76
 Alrayes, Lamya P2-15
 Alsaffar, Hussain P3-183, P3-20, P3-76
 Alsagheir, Afaf P2-15
 Alsaghier, Afaf P3-26
 Alshafey, Mohammed P3-20
 Alshahrany, abdullah P2-56
 Alshahrany, nouf P2-56
 Alshidhani, Azza P3-76
 Alshukaili, Maha P3-76
 Altinoglu, Umut P1-306
 Altube, Mercedes P1-72
 Altunoglu, Umut P1-134
 Altunoğlu, Umut P1-390, P2-195
 Alulovska, Natasa P3-248
 Alvi, Sabah P1-6, P2-248, RFC10.1, RFC13.2
 Alwadiy, Faisal P1-318, P2-84
 Alyaarubi, Saif P3-20, P3-76
 Alyafei, fawzia P1-313
 Alyafei, Fawzia P2-183
 Amano, Naoko P1-275
 Amarasingha, Shenali P2-63
 Amarasingha, Shenali Anne P1-317
 Amarri, Sergio FC3.2, RFC14.3
 Amary, Fernanda P3-196
 Amat-Bou, Montse FC15.5
 Amemiya, Shin RFC1.1
 Amin, Amina FC12.5
 Amin, Nadia P2-248
 Amin, Rakesh RFC5.4
 Amorim, Marta P2-130, P3-239
 Amselem, Serge P1-257, P1-80, P3-200
 An, Yu RFC6.1
 Anadol, Elvan P1-255
 Anastasovska, Violeta P3-248
 Anderson, Yvonne P1-50
 Andersson, Anna-Maria T4
 Andreas, Gleiss P1-76
 Andreeva, Elena P1-121
 Andres, Carlos P2-277
 Andrew, Ruth FC13.2
 Andrzej, Lewinski P1-77
 André, Julia RFC2.2
 Angela, Huebner P1-66
 Angelini, Sabrina RFC14.3
 Anik, Ahmet P1-162, RFC8.5
 Anikiev, Alexander P1-121, RFC5.3
 Ankarberg-Lindgren, Carina RFC11.4
 Anolue, Mirabel P3-294
 Anoprienko, Olena P3-237
 Anselmi, Federica P1-409
 Antoniazzi, Franco P1-5, RFC9.3
 Antonini, Sonir FC13.3, RFC13.4
 Antoniou, Maria-Christina P1-424
 Antosz, Aleksandra P1-53
 Antunes, Ana P1-253, P3-318
 Anzo, Makoto P2-217
 Aoki, Masako P1-333
 Aouida, Mustapha P1-189
 Aoyama, Kohei FC5.6, P3-173
 Apostolaki, Despoina P3-275
 Apperley, Louise P1-314, P2-180, P2-190
 Aquilina, Kristian RFC11.1
 Ara Montojo, Fatima P1-374
 Ara Royo, Ignacio P2-128
 Arab Sadeghabadi, Zahra P1-341
 Aragonés, Angel RFC1.4
 Arai, Yuto P2-30
 Arash Yilmaz, Aslihan FC10.6, P1-284, P1-342, P1-348, P2-198, P3-180
 Arbesú Saracho, Cecilia P1-272
 Arcari, Andrea Josefina LB-7
 Ardisia, Carmela LB-22
 Arrestova, Anzhelika P2-221
 Argente, Jesús FC14.3, FC15.6, FC8.2, FC8.4, P1-100, P1-376, P2-129, P2-239, P3-276, RFC14.1, S5.1
 Arhan, Ebru P2-103
 Arienz, Maria Rosaria FC4.4
 Arimasu, Yu FC5.6
 Ariza Jimenez, Ana Belen P3-278
 Arlt, Wiebke P1-162
 Arman, Ahmet P1-175, P1-176
 Armağan, Coşkun P1-28
 Aronson, A. Stefan P1-250
 Aronson, Stefan P1-119
 Arozarena, Maria P1-410
 Arrigoni, Marta P1-68, RFC9.6
 Arroyo-Díez, Francisco Javier P3-306
 Arslan Ateş, Esra P3-202
 Arslan, Gulcin P3-124, P3-2
 Arslan, Gülcin P1-27, P2-12, P3-19, P3-233
 Arslanian, Silva S9.3
 Arslanoglu, Ilknur P3-62
 Artati, Ratna P3-207
 Artemova, Alla P2-212
 Artola, Elena P2-279
 Artuso, Rosangela P1-194, P1-336, P2-181
 Arya, Archana P2-113, P2-141, P3-57
 Arya, Ved Bhushan P1-215
 Arzumanyan, Angelina P2-96
 Asahina, Izumi P1-170
 Ascaso Matamala, Angela Marina P1-229
 Ascenti, Giorgio P1-346, P3-10
 Ascunce, Nieves P2-277
 Ashour, Khaled P2-120
 Asmahane, Ladjouze P1-292, P2-161
 Assefi, Aria P2-167
 Assefi, Aria Reza P1-82
 Assens, Maria T4
 Astashova, Ekaterina P2-219

- Astudillo, Patricio P1-37
 Ata, Aysun P3-217, RFC6.4
 Ata, Pinar P1-175, P1-176
 Ata, Pinar P2-52
 Atapattu, Navoda P3-271
 Atapattu, Navoda P1-10, P1-157, P2-80, P3-291, P3-304, P3-321, P3-322
 Atar, Müge P2-268, P2-291, P2-291
 Atay, Enver P1-208
 Atay, Zeynep P1-402
 Atay, Zeynep FC7.5, P1-162, P1-208, P1-60
 Atef, Abeer P2-256
 Ates, Esra P2-25
 Ateş, Oğuz P2-284
 Atger-Lallier, Laura RFC3.2
 Athanasouli, Fani P3-102, P3-126
 Atik, Tahir RFC6.4
 Atlas, Gabby P1-124
 Attapatu, Navoda P1-167
 Attasi, Abdul Aleem P1-161
 Auderset, Anne P1-29
 Audrain, Christelle FC2.3, P1-23
 Audrey, Matallana P3-199
 Auerbach, Adi P3-16
 Auger, Martin P1-18
 Augustin, Adrien RFC4.4
 Augusto Jorge, Alexander P1-135
 Augustus, Rhian P2-108, P3-104
 Aurbach, Adi P3-296
 Auriche, Morgane P1-303
 Avbelj Stefanija, Magdalena P1-109, T12
 Avci, Ayse P1-411
 Avci, Sahin P1-134
 Avci, Şahin P1-390
 Aversa, Luis P1-410
 Aversa, Tommaso P1-106, P1-346, P1-401, P1-422, P1-53, P2-182, P2-186, P3-10, P3-164
 Avnieli Velfer, Yael P2-115
 Avnon Ziv, Carmit P3-296
 Avnon-Ziv, Carmit P1-128
 Avnon-Ziv, Carmit P3-16
 Avula, Shivaram P1-102
 Aw, Marion P1-44
 Awadalla, Shokery P3-127
 Ay, Gulsevinc P1-117
 Aya, Misaki P1-275
 Ayadi, Fatma P3-206
 Ayarzabal, Victor LB-26
 Ayaz, Ayse Burcu P2-270
 Aycan, Zehra P2-101
 Aycan, zehra FC10.6
 Aycan, Zehra P1-160, P1-181, P1-255, P1-284, P1-330, P1-342, P1-348, P2-119, P2-137, P2-198, P2-234, P3-180, P3-225, P3-8, P3-9
 Aydin, Banu P1-248
 Aydin, Ferah P1-89
 Aydiner Karakoc, Elif P1-116
 Aydın, Cansever LB-14
 Aydın, Murat P2-137
 Aygün, Ayşe LB-14
 Aylwin, Simon P2-231
 Ayoade, Kayode P1-288
 Ayoola, Omolola P1-38
 Ayrancı, İlkay P1-143, P1-245, P1-308, P1-321, P3-106, P3-159, P3-182, P3-215, P3-226
 Aytaç Kaplan, Emel Hatun P1-353
 Ayvaz, Deniz Cagdas P1-239
 Ayyavoo, Ahila P1-312
 Azaretzky, Miriam P3-283
 Azcona, Cristina P1-192
 Azimova, Shaknoza P3-112
 Azza Nasser, Al Shidhani P1-222
 Azzolini, Sara LB-22, P1-418
- B**
- Babiker, Amir P1-161, P2-31
 Babiker, Omer P2-67
 Babinskaya, Svetlana P2-157
 Bachega, Tania P1-157, P1-167
 Bachega, Tania SS P1-10
 Bachmann, Nadine P1-211
 Bachmann, Sara FC7.2, P1-29
 Bacila, Irina-Alexandra P1-10, P1-6, RFC13.2
 Backeljauw, Philippe P2-178
 Bacopoulou, Flora P1-198, P1-238, P1-242, P2-213, P2-58, P3-275, P3-302
 Badawi, Nora P2-87
 Badawy, Haytham P1-413
 Badolato, Raffaele P2-8
 Bae, Mi Hye P1-429
 Bagci, Pelin P2-25
 Baghersalimi, Adel P3-72
 Bailez, Marcela P2-259
 Bajpai, Anurag P2-73, P3-227
 Bakker, Nienke FC12.3
 Balasubramanian, Ravikumar S11.1
 Balbi, Viviana P1-8
 Bald, Martin P1-51
 Baldini Ferroli, Barbara P1-300
 Baldinotti, Fulvia P3-232
 Balducci, Anna P1-378
 Balikova, Irina P2-237
 Ballantyne, Angela P1-279
 Ballerini, María Gabriela P1-72
 Balosakova, Marcela P2-168
 Balsamo, Antonio P1-10, P1-157, P1-167, P1-300, P1-97, RFC10.1
 Bancalari, Rodrigo P1-338
 Banchini, Giacomo P2-150, P3-133
 Banerjee, Indie P1-205
 Banescu, Claudia P1-358
 Bang, Peter P1-212, P1-214
 Baquer, Najma P1-130
 Barakizou, Hager P1-26, P3-196
 Baran, Rıza Taner P1-207, P1-254
- Baranowski, Elizabeth S. P1-162
 Barbi, Egidio LB-18, P3-168, P3-244
 Barbieri Marmo, Denise P1-85
 Barbieri, Flavia P2-287
 Barbosa, Julio P2-196
 Barbosa, Julio Montes P2-57
 Barbu, Carmen Gabriela P1-202
 Barc, Deniz P1-117
 Barczynski, Edwin LB-19
 Bardai, Ghalib RFC6.3
 Bardugo, Aya P2-123
 Barera, Graziano P1-423, P2-298, P3-144, P3-205
 Barg, Ewa LB-19
 Bargiacchi, Sara P1-194, P1-336
 Bargman, Graciela P1-410
 Baris Feldman, Hagit P1-32
 baris, safa P1-116
 Baris, Tugba P1-162
 Barja-Fernández, Silvia P1-345
 Barkas, Konstantinos RFC11.1
 Barnard, Lise P1-162
 Barnes, Michael FC15.4
 Barnes, Michael R. FC8.5
 Barnett, Tracie P1-337
 Barnett, Tracie A. P1-197, P1-57
 Baron, Jeffrey FC15.1, RFC15.5
 Baronio, Federico P1-106, P1-167, P1-300, P2-227, P2-232
 Barosi, Anna FC6.6, P1-23
 Barquero, Paula P2-194
 Barreda, Ana Coral RFC1.4
 Barreiro, Jesus P2-61
 Barrett, Tim P1-370
 Barrios, Vicente FC15.6, FC8.4
 Barthlen, Winfried FC9.6
 Bartmann, Peter FC9.4
 Barton, John S P2-253
 Bas, Firdevs P1-134, P1-159, P1-306, P1-390, P2-270, P2-45
 Bas, Serpil P1-273
 Basaran, Seher P1-134, P1-306
 Bashamboo, Anu FC10.3, FC10.4, P1-127, P2-272, P2-244
 Bashnina, Elena P3-150, P3-55
 Bassols, Judit FC9.3, P1-193, P1-56, P2-127, RFC4.3, T1
 Bastianello, Maria P1-240
 Batista, Rafael L P1-262
 Batista, Rafael Loch P1-270, P3-219
 Batsakoutsa, Alkistis P3-236
 Battelino, Tadej FC14.5, P1-109, P1-227, T12
 Batzios, Spyros P2-143
 Baudrand, René P1-338
 Bauer, Jana Leonie FC6.5
 Bayburdyan, Gayane P3-289
 Bayram, Yavuz P1-273
 Bayramoglu, Elvan P2-119, P2-137

- Bayramoğlu, Elvan P1-160, P1-330, P1-348, P2-234, P3-225, P3-9
 Baysal, Birsen P1-254
 Baysal, Ozlem P3-65
 Baz, Ouidad P2-280, P3-146
 Bazdarska, Yulia P2-174
 Bazdarska, Yuliya P2-149
 Baş, Firdevs P1-145, P1-236, P2-137, P2-195
 Başaran, Seher P1-390
 Beauloye, Véronique P2-153
 Beccaria, Kevin P2-226
 Beccherle, Federico RFC9.3
 Bechtold, Susanne FC7.6
 Beck Jensen, Rikke FC14.2
 Becker, Bettina FC6.5
 Becker, Marianne P1-179
 Beckers, Albert PL7
 Beckert, Michael FC14.4
 Bedecarrás, Patricia LB-7, P1-410
 Bedoin, Jacques P1-371, RFC14.6
 Bedoya, Juan José P3-119
 Beerendonk, Catharina P1-377, RFC12.1
 Beeri, Rachel P3-296
 Beghini, Marianna RFC11.5
 Begijn, Dominique RFC13.3
 Beglinger, Svetlana FC7.2
 Behar, Doron P1-128
 Belabas, Lynda P2-280
 Belabed, Wafa P3-221
 Belcheva, Milena P1-350
 Belghith, Neila P3-221
 Belgorosky, Alicia P1-129, P2-167, P2-259
 Belguith, Neila P1-94, P3-229
 Belisle, Alexandre RFC6.3
 Bellafiore, Marianna P1-392, P1-95
 Bellastella, Giuseppe T3
 Belli, Gilda P3-43
 Bellido More, Candy FC13.3
 Bello, Rachel T17
 Bellone, Simonetta P2-171
 Beltrand, Jacques P2-226
 Ben Becher, Saayda P2-77, P3-238
 Ben Chehida, Amel P2-77
 Ben Hammouda, Hachmi P3-91
 Ben Mrad, Fatma P3-216, P3-221
 Ben Othman, Wafa P2-39, P3-229, P3-252
 Ben Rhoum, Bochra P3-229
 Ben Rhouma, Bochra P3-221
 Ben Yakhlef, Salma P3-86
 Ben-Ami, Michal RFC7.5
 Ben-Sira, Liat P1-397
 Ben-Skowronek, Iwona P2-286
 Benatti, Maria Teresa P3-277
 Benavides-Boixader, Anna P1-193
 Bendor, Cole P2-123
 Benhalla, Nafissa P3-113
- Benouis, Amina P3-308, P3-329, P3-331, P3-332
 Benson, Joanna P1-384
 Benyakhlef, Salma P3-240
 Berardi, Alberto RFC9.6
 Berberoglu, Merih FC6.4, P2-137, P3-8
 Bercovich, Dani P1-105, P3-200
 Bercovitch, Dani P2-19
 Bereket, Abdullah P1-116, P1-3
 Bereket, Abdullah P1-159, P1-162, P1-175, P1-176, P1-273, P1-402, P1-53, P2-25, P2-52, P3-202, P3-80, RFC8.5
 Berenstein, Ariel J. P1-410
 Berenztein, Esperanza P1-129, P2-259
 Bergada, Ignacio P1-152
 Bergadá, Ignacio FC14.1, LB-7, P1-359, P1-410, P1-72
 Bergmann, Carsten P1-211
 Berkay, Ezgi P2-5
 Bernardi, Stella LB-18
 Bernardo, Maria Teresa LB-16, P3-315
 Bernasconi, Sergio P2-150, P3-133
 Berr, Zivan P2-123
 Berrade, Sara P2-277
 Berrade-Zubiri, Sara P3-116
 Berseneva, Olga P3-150, P3-55
 Bertalan, Rita FC10.3, FC10.4, P2-244
 Bertelloni, Silvano HDI 2.1, P1-262, P3-232
 Bertholt Zuber, Laura P2-74
 Bertholt Zuber, Maria Laura P2-102
 Bertok, Sara T12
 Bertola, Debora R RFC8.4
 Bertoncelli, Natascia RFC9.6
 Bespaluk, Daria P1-357
 BESPEED, and the members of P2-153
 Bessa, Danielle RFC8.2
 Betsi, Grigoria P3-192
 Bettendorf, Markus FC5.5, P1-365, P2-269
 Bettini, Alessandra P1-79
 Bezlepkinsa, Olga P1-356, RFC5.3
 Beń-Skowronek, Iwona P2-134
 Bhat, Kavitha P2-211
 Bhattacharjee, Rana P1-276
 Biason-Lauber, Anna FC10.2, FC10.5, P1-264, P1-412, P2-271, RFC10.5
 Bideci, Aysun P1-103, P1-351, P2-103, P2-44, P3-56
 Biedermann, Rainer RFC15.5
 Bielikova, Svetlana P2-168
 Bielsky, Laila P1-240
 Biester, Torben P1-179
 Biggs, Janene FC7.4
 Bigi, Elena RFC3.5
 Bignon-Topalovic, Joelle FC10.3, FC10.4
 Bilgic Eltan, Sevgi P1-116
 Bilharinho Mendonça, Berenice P1-135
 Bilici, Esra P3-8
- Billiris, Antonis P2-140
 Binder, Gerhard FC6.5, P1-12, P1-231, P1-380, RFC2.3
 Bindiganavle, Aparna P2-62
 Binou, Maria P3-96
 Birkebaek, Niels P1-157, P1-167, RFC10.1
 Birkebaek, Niels H P1-10
 Birkebaek, Niels H. P1-136, P1-319
 Birraux, Jacques P2-264
 Bisbinas, Vasiliki P3-184, P3-53
 Bisgin, Atil P1-411
 Bisi-Onyemaechi, Ada P2-199
 Bitkin, Eda C. P1-162
 Bizerea-Moga, Teofana Otilia P3-303
 Bizzarri, Carla P1-247, P1-300, P1-386, P2-225
 Bjelke, Mads P1-363
 Bjerknes, Robert P1-110
 Black, Sarah P2-293, P2-36
 Blackburn, James P1-113, P2-236
 Blair, Jo P2-190
 Blair, Joanne P1-102, P1-246, P1-259, P2-180
 Blankenstein, Oliver P1-10, P1-156, P1-157, P1-167
 Blankers, Lizette P1-47
 Blasetti, Annalisa P3-274, P3-314
 Blauwblomme, Thomas P2-226
 Bloch, Stav LB-5
 Blouin, Stéphane FC6.1
 Bluemel, Peter P2-187
 Blum, Werner F P3-133
 Blum, Werner F. P2-150
 Bocchi, Federica RFC7.6
 Bocheva, Yana P1-350, P2-149, P2-174
 Bochkova, Larisa P2-148
 Bodamer, Olaf P1-225
 Boden, Matthew G. FC15.1
 Bodieu Chetcha, Adele P3-125, P3-137
 Boelaert, Kristien P1-286, P1-426
 Boelen, A. RFC9.2
 Boer, Pieter RFC2.5
 Boettcher, Claudia P2-3
 Bogova, Elena P1-356
 Boitsios, Gramatina P2-237
 Boizeau, Priscilla RFC3.2
 Bolboacă, Sorana D. P3-109
 Bolle, Stéphanie P2-226
 Bolotova, Nina P1-133
 Bolshova, Olena P3-262
 Bolu, Semih P2-137
 Boncompagni, Alessandra P1-262, RFC7.6, T19
 Bonfig, Walter FC7.6, P1-10, P1-157, P1-167, RFC10.1
 Bongsebandhu-phubhakdi, Chansuda P2-243
 Boni-Mikats, Andrea FC2.4
 Bonilla-Jaime, Herlinda P1-43
 Bonmatí-Santané, Alexandra FC9.3

- Bonsón, Javier RFC14.1
 Bonvicini, Federico RFC14.3
 Boogaard, Merel W. P1-228
 Boomstra, Dorret FC13.2
 Boot, Annemieke FC2.1, FC2.2, RFC2.5, SS1.1
 Boquete, Carla P3-283
 Boquete, Hugo P3-283
 Borchers, Joonatan FC3.6
 Bordon, Victoria P1-171, P2-105
 Borges, Catarina LB-16, P3-315
 Boros, Emese P1-86, P2-237
 Borrello, Simona P2-182, P3-164
 Borysewicz- Sańczyk, Hanna P1-148
 Borysewicz-Sanczyk, Hanna P2-278
 Borysewicz-Sańczyk, Hanna P2-36, P3-167, T2
 Bos, Melanie P1-388
 Bosch, Laura RFC9.4
 Bosch, Zelmira P1-282, P3-107
 Bosi, Emanuele P1-194, P1-336, P2-181
 Bossini, Benedetta P3-168
 Bossowska, Anna P2-293
 Bossowski, Artur FC5.2, P1-148, P2-278, P2-293, P2-36, P2-72, P3-167, T2, p1-421
 Bottari, Antonio P1-346, P3-10
 Bottaro, Giorgia P1-260, P1-58
 Bottero, Arianna P2-8
 Boucenna, Hamza P3-113
 Bouchair, Nadhira P3-330
 Bouchair, Nadira P3-189
 Bouferoua, Fadila P3-113
 Bouga, Maira FC9.5
 Boughaleb, Hasnae T9
 Bougnères, Pierre P1-213, RFC15.1
 Boukhedouma, Nabila P3-113
 Bouki, Katerina P3-192
 Bouloumié, Anne FC4.2
 Bourdeaut, Franck P2-226
 Bourdrez, Petra LB-12
 Bourgeois, Marie P2-226
 Boussoffara, Raoudha P2-60
 Boussetta, Khedija P2-77
 Bousyf, Bouchra P2-274
 Boutilbi, Narjess P3-189
 Bouthors, Thérèse P1-424
 Bouvattier, Claire P1-213, P1-269
 Bouzerar, Zahir P1-292, P3-128
 Bouzerar, Zair P1-296
 Bowen, Philippa P2-260
 Boyadzhiev, Veselin P2-174, T13
 Bozinovski, Georgi P2-216
 Bozzola, Mauro P2-171
 Braat, Didi P1-377, RFC12.1
 Brachet, Cécile P1-86, P2-237
 Brad, Giorgiana Flavia P2-116, P3-303
 Brain, Caroline RFC5.4
 Brandsma, Annelies P1-46
 Brandt, Agnieszka P3-187
 Brandt, Stephanie P1-210, RFC11.5
 Brandt-Varma, Agnieszka P2-100, P3-66, P3-81
 Braovac, Duje P2-179
 Braslavsky, Debora FC13.5
 Braslavsky, Débora P1-72
 Brassier, Anaïs LB-11
 Bratina, Nataša P1-109
 Braune, Katarina P1-156
 Brauner, Raja FC10.3, FC10.4
 Bray, Dr Dominic P2-88
 Brazovskii, Konstantin P1-328
 Breil, Thomas P1-365
 Brener, Avivit P1-347, P2-6
 Bressiani, Marina P3-35, P3-40
 Breunis, Leonieke RFC2.5
 Breuring, Dieter P3-297
 Brianza-Padilla, Malinalli P1-43
 Brichta, Corinna Melanie P2-32
 Briosa, Filipa P3-239
 Briot, Karine FC2.3
 Brioude, Frederic P1-218, P1-257
 Brioude, Frédéric FC12.1, P1-80
 Brito, Vinicius RFC8.2
 Brod, Meryl P1-235, P1-371, P1-84, RFC14.6
 Brovin, Dmitriy P1-121, P2-201, RFC5.3
 Bruce, Aisha P2-34
 Brue, Thierry P3-269
 Brugières, Laurence P2-226
 Brunetti, Giacomina RFC6.2
 Bruno, Rocco P2-182, P3-164
 Brunova, Jana FC6.3
 Brusa, Jessica P1-392, P1-95
 Bruserud, Ingvid S. P1-258
 Bruserud, Ingvild P1-267
 Brusgaard, Klaus P1-211, P1-319
 Bruzzi, Patrizia P1-185, P2-232, RFC3.5, RFC7.6, T6
 Bryce, Jillian P1-157, P1-167, P1-262, RFC10.1, RFC3.1
 Brzhezinskaya, Lubov P2-261
 Buchanan, Charles P2-231
 Buchanan, Charles R P1-215
 Budge, Helen P1-352
 Bueno Lozano, Gloria P1-229
 Bueno, Ana Carolina FC13.3
 Bueno, Gloria P1-33, P1-345, P3-119
 Bufalo, Lorenzo P1-409
 Buganza, Raffaele P1-20, P1-400
 Bugi, Meda Ada P2-116
 Bugsinskaya, Nadiia P2-106
 Bugrul, Fuat P1-116
 Buhl, Joseph P1-30
 Bui Phuong, Thao P3-21, P3-260
 Bui, Helen FC5.4, P2-84
 Bui, Phuong Thao P2-7
 Bujan, Maria Marta P1-240
 Bukin, Sergey P3-253
 Bulus, Ayse Derya P1-181
 Bulut, Huri P1-396
 Bundak, Ruveyde P3-149
 Buonocore, Federica FC10.3, FC11.2, P2-2
 Burckhardt, Marie-Anne FC7.2
 Burdea, Liliana P3-251, P3-52
 Burdet, Sofia P1-240
 Burren, Christine P P2-152, P2-253
 Busani, Luca P1-260, P1-58
 Busch, Alexander P1-114, P1-399
 Busch, Alexander S FC11.6
 Busch, Alexander S. FC14.2
 Bushan Arya, Ved P2-231
 Busiah, Kanetee LB-11
 Busiah, Kanetee P1-424, P2-226
 Buzi, Fabio P2-8
 Buzzigoli, Emma P1-260, P1-58
 Buğrul, Fuat P3-220, P3-3
 Böber, Ece P1-285
 Böber, Ece P1-28, P2-284, P3-198, P3-250
 Böttcher, Claudia P3-83
 Błaszczyk, Ewa P1-373
- C**
 C-G Hombría, James FC10.2
 Cabanas, Paloma P2-61
 Cabrera, Claudia FC15.4
 Cabrera, Claudia P. FC8.5
 Caiulo, Silvana P1-420, P1-423, P2-298
 Cakir, Meltem Didem P3-65
 Calabrese, Olga T6
 Calaminus, Gabriele P1-398
 Çalan, Özlem Gürsoy P1-335
 Calandra, Erika T3
 Calandrino, Andrea P1-252
 Calcaterra, Valeria P1-323, P1-428, P2-64, P3-115, P3-98
 Calevo, Mariagrazia RFC12.5
 Calliari, Luis Eduardo P2-194
 Caluseriu, Oana P3-234
 Camacho-Hübner, Cecilia P1-379, P1-89
 Camassola, Bruna P3-40
 Camilot, Marta P1-5, RFC9.3
 Campbell, Fiona P1-327
 Campbell, Matthew MTE 6
 Campderros, Laura FC4.3
 Campi, Veronica P1-364
 Campino, Carmen P1-338
 Campos, Angel P2-145, RFC1.4
 Campos, Ariadna P2-164
 Camós-Carreras, Maria P1-56
 Çamurdan, Orhun P1-103, P1-351, P2-103, P2-44, P3-56
 Can Thi Bich, Ngoc P3-260
 Cananguez, Arlen A P3-29
 Candler, Toby P1-123
 Canelles, Sandra FC15.6, FC8.2
 Cangur, Sengul P3-62
 Cangül, Hakan P1-145
 Cannavò, Laura P2-147

- Cannavò, Laura RFC5.1
 Cano, Carmen RFC3.5
 Canton, Ana RFC8.2
 Cao, Bingyan P1-316, P2-177
 Capaci, Merve P2-240
 Capalbo, Daniela P1-45
 Capalbo, Donatella P1-300, P2-160, P2-287
 Capasso, Mario P1-362
 Capdevila, Nuria P1-382
 Cappa, Marco P1-14, P1-386, P1-97, P2-225
 Capri, Yline P1-139
 Carcavilla, Atilano RFC1.4
 Cardella, Francesca P2-192
 Cardinale, Antonella P1-362
 Carel, Jean-Claude RFC3.2
 Carel, Jean-Claude FC10.3
 Cariboni, Anna FC8.5
 Carilo, Maria Adelaide P3-232
 Carli, Fabrizia P1-260, P1-58
 Carlsson, Martin P1-379, P1-89
 Carmi, Doron LB-5
 Caron, Philippe P1-150
 Carpenter, Thomas O. FC2.1, FC2.2
 Carpino, Andrea P2-208
 Carrascosa, Antonio P2-164
 Carreras-Badosa, Gemma P1-56, RFC4.3
 Carrozzi, Marco P3-244
 Cartault, Audrey P1-132, P1-139, P1-269, T8
 Caruso-Nicoletti, Manuela P1-247, P2-75, P3-5
 Carvajal, Cristian P1-338
 Casalini, Emilio RFC12.5
 Casano, Simona P2-132
 Casanueva, Felipe F P1-345
 Casari, Giulia P3-98
 Cassio, Alessandra P1-111, P1-401, P2-171, P2-227, P2-92
 Castagna, Andrea P2-8
 Castanet, Mireille LB-4
 Castelao, Cecilia P1-345
 Castets, Sarah P3-269
 Casto, Celeste P2-182
 Castorani, Valeria P3-274
 Castro, Julia Fernanda FC14.1
 Castro, Laura P1-364
 Castro, Margaret FC13.3
 Castro, Sofia P1-253
 Castro-Correia, Cíntia P2-14, P2-4
 Castro-Feijoo, Lidia P2-61
 Casula, Letizia P2-132
 Catalán, Ana P1-192
 Catellani, Cecilia FC3.2, RFC14.3
 Catena, Helen P1-9
 Catli, Gonul P1-162
 Cattoni, Alessandro P1-98
 Caturegli, Patrizio P1-251
 Cavada, Gabriel P1-338
 Cavarzere, Paolo P1-5
 Cavarzere, Paolo RFC9.3
 Cave, Tami P1-50
 Cavin, Rosalie P1-425
 Cavé, Hélène P1-139
 Cayir, Atilla P1-207, P1-71
 Cañas, Mª Teresa P2-239
 Çatlı, Gönül P1-143, P1-245, P1-308, P1-321, P1-335, P3-106, P3-159, P3-182, P3-215, P3-226
 Çayır, Atilla P1-241
 Ceccarelli, Pier Luca P1-417
 Cecchetti, Valeria P2-298
 Cecconi, Antonella P3-43
 Cekin, Necmi P1-411
 Celaya, Patricia P3-276
 Celen, Safiye Suna P2-235
 Celik, Gonca P1-411
 Celis Ayala, Luciana P1-82
 Cellini, Monica RFC3.5
 Cena, Hellas P1-323, P3-115, P3-98
 Cenciarelli, Valentina P1-185, RFC7.6
 Cengiz Özürt, Beyhan P3-285
 Censi, Simona P1-418
 Ceran, Aysegul P3-8
 Cerbone, Manuela FC11.1, P1-120
 Cerioli, Andrea P2-150, P3-133
 Cerit, Kivilcim P2-25
 Cesur, Yaşar P1-396
 Cetin, Tugba P3-8
 Cetinel, Nesrin P1-117
 Cetinkaya, Semra P1-181, P1-255
 Cetinkaya, Semra FC10.6
 Cetinkaya, Semra P2-101
 Çetinkaya, Semra P1-160, P1-284, P1-330, P1-348, P2-119, P2-198, P2-234, P3-180, P3-225, P3-9
 Chabchoub, Imen P1-322
 Chabowski, Adrian p1-421
 Chae, Hyun-Wook LB-23
 Chahboune, Ahmed P2-280
 Chaliasos, Nikolaos P1-54
 Challal, Anna P1-54
 Champion, Michael P1-177
 Chan, LF RFC13.5
 Chandler, Chris RFC11.1
 Chang, Guoying P2-188, T20
 Chang, Yen-Ch'ng RFC11.1
 Chang, Zhuo P3-24
 Chanprasertyothin, Suwannee P1-201
 Chantot-Bastaraud, Sandra FC12.1, P1-218
 Chao-Hsu, Lin P3-245
 Chaochun, Zou P2-135, P3-169
 Chapla, Aaron P2-79
 Chapman, Karen RFC3.4
 Chapman, Simon A P1-215
 Chareca, Cinthia P1-82
 Chareca, Cinthia D P2-167
 Charfi, Nadia P2-266, P2-39, P3-216, P3-221, P3-25, P3-252
 Charmandari, Evangelia P2-140, P3-101, P3-96
 Chatelain, Pierre FC12.5
 Chatterjee, Krishna P1-286
 Chatterjee, Sumana RFC14.4
 Chaturvedi, Deepti P3-183, P3-23
 Chaussain, Catherine FC2.3
 Chawla, Meghna P3-162
 Chawla, Meghna P3-171
 Chaychenko, Tetyana P2-106, P3-121
 Chechelnitskaya, Serafima P2-109
 Cheetham, Tim FC15.1, FC5.1, MTE 7
 Cheetham, Timothy P1-6, RFC13.2
 Chelghoum, Imane P2-280
 Chen, Da P3-14
 Chen, Haixia P2-191
 Chen, Hong FC1.1, P1-278, P1-297, P3-223
 Chen, Hongshan P3-151, P3-6
 Chen, Hongshan P1-183, P1-61, P2-114, P3-193, P3-222
 Chen, Hongshan P3-241, P3-44
 Chen, I-Shan FC5.6
 Chen, Jiajia P2-222
 Chen, Jiajia P1-316, P1-76
 Chen, Li-Min P1-324
 Chen, Lin-qi P3-145
 Chen, LinQi P3-208
 Chen, Linqi P2-294
 Chen, Qiong P2-55, P3-12
 Chen, Qiu P3-193
 Chen, Qiuli P3-151, P3-6
 Chen, Qiuli P2-114, P3-222
 Chen, Qiuli P3-241, P3-44
 Chen, Rui-min P3-145
 Chen, Ruimin P1-191, P1-224, P1-63, P2-177
 Chen, Shao-ke P3-145
 Chen, ShaoKe P2-121
 Chen, Shijun P1-224
 Chen, Shu P2-293, P2-36
 Chen, Ting P2-294
 Chen, Wei FC15.2
 Chen, Xi P2-191
 Chen, Xiaobo P3-324, P3-325
 Chen, Xiuli P2-294
 Chen, Xuefeng P2-121
 Chen, Yao P1-225, P1-277, P2-188, T20
 Chen, Yongxing P2-55, P3-12
 Chen, Yuling P1-277
 Chen, Suet C. FC2.5
 Cheng, Adam P1-9
 Cheng, Biwen P3-245
 Cheng, Cheng P3-241
 Cheon, Chong Kun P1-385, P1-62, P3-13
 Cheong, Hae Il RFC2.1
 Chernenkova, Yurii P3-177
 Chertin, Boris P1-128

- Chertok, Elena FC14.4
 Cherubini, Valentino P1-401
 Chesi, Elena P2-150
 Cheung, Moira P1-177, P3-270, P3-327
 Chevalier, Claudia P1-425
 Chevenne, Didier RFC15.6
 Chi Dung, Vu P2-133, P3-141
 Chiarelli, Francesco HDI1.3, LB-13, P3-274, P3-314
 Chiarello, Paola P2-300
 Chiarito, Mariangela P1-300, P3-232
 Chiarpenello, Javier P2-167
 Chiavaroli, Valentina FC7.4, YI1.2
 Chiesa, Ana P1-152
 Chikani, ugo P2-199
 Chikermane, Ashish P1-426
 Chikulaeva, Olga P2-157
 Chime, Paschal P2-199
 Chin, Xinyi P1-302
 Chiu, Chiao-Fan P1-137
 Cho, Ja Hyang P3-103
 Cho, Kyoung Soon P2-166, P2-85
 Cho, Kyoungsoon P1-233, P2-218, P3-117
 Cho, Sung Yoon P2-158, P2-282
 Cho, Won Kyoung P2-85, P3-174
 Cho, Wonkyoung P2-166
 Cho, Wonkyoung P1-233, P2-218, P3-117
 Cho, Wonkyung P2-122
 Choenni, Vandhana RFC13.3
 Choi, Han-saem FC8.6
 Choi, Im Jeong P1-385, P1-62, P3-13
 Choi, Jin Ho LB-23
 Choi, Jin-Ho P1-101, P2-209, P3-179
 Choi, Yujung P1-233, P2-218, P2-85, P3-117
 Choi, yujung P2-122
 Choo, Kelvin P1-65, P2-151
 Chou, Yu-Yu P1-383
 Choukair, Daniela FC5.5, P1-365, P2-269
 Chouvarda, Ioanna FC7.1
 Chowdhury, Subhankar P1-276
 Chowen, Julie FC14.3, P1-100, RFC14.1
 Chowen, Julie A. FC15.6, FC8.2, FC8.4
 Chrisp, Georgina P1-299
 Christesen, Henrik P1-211
 Christesen, Henrik P3-29
 Christians, Julian FC14.3, RFC14.1
 Christoforidis, Athanasios P1-166
 Chrousos, George FC1.3, FC13.6, P2-204, P3-181
 Chrysis, Dionisios P1-379
 Chrysoulaki, Maria P3-192
 Chrzanowska, Krystyna P3-163
 Chueca, Maria J. P2-277
 Chueca, María P1-192
 Chueca-Guindulain, María P3-116
 Chugh, Vasundhara P2-113, P2-141, P3-57
 Chugunov, Igor P1-357
 Chukwumerije, Chidinma P3-311
 Chumachenko, Tetyana P2-106
 Chumak, Svitlana P3-92
 Chung, Bon-Chu P1-162
 Chung, Eun Jae FC5.3
 Chung, Hye Rim LB-21
 Chung, In-Hyuk P2-139
 Chung, Lindsey Yoojin LB-15, P1-268, P2-283, P3-123
 Chung, Myung Hee P3-34
 Chung, Myung Hee P3-131
 Chung, Sochung LB-23, P2-139, P3-38
 Chung, Woo Yeong P3-15
 Chunlin, Wang RFC5.6
 Chuperkova, Jivka P2-149
 Ciaccio, Marta P1-249
 Ciampalini, Paolo FC7.3
 Ciancia, Silvia P1-185, T6
 Cianfarani, Stefano FC7.3, P1-260, P1-386, P1-58
 Ciccarelli, Gian Paolo P2-160
 Ciccone, Sara P2-225, P3-17
 Çiçek, Dilek P3-67, P3-134, P3-263
 Çığ, Esranur P2-268
 Ciljakova, Miriam P2-168
 Cilleruelo, M. Luz P3-276
 Cilsaat, Gizem P1-159, P1-306
 Cima, Luminita-Nicoleta P1-202
 Cinalli, Giuseppe RFC11.2
 Cinarli, Feride P1-394, P2-275
 Cinaz, Peyami P1-103, P1-351, P2-103, P2-44, P3-56
 Cinek, Ondřej P2-69
 Çinici, Emine P1-81
 Cioffi, Daniela RFC11.2
 Ciofi, Daniele P1-107, P1-79, P3-43
 Cionna, Cecilia FC11.1
 Circo, Eduard P2-207
 Cirillo, Francesca FC3.2, RFC14.3
 Cirillo, Grazia FC4.4, P1-354, P1-45, P1-93
 Cirillo, Grazia P1-111
 Cirillo, Mario RFC11.2
 Çızmecioğlu, Filiz Mine FC9.5
 Claahsen - van der Grinten, Hedi P1-269
 Claahsen - van der Grinten, Hedi L P1-10
 Claahsen van der Grinten, Hedi P1-157
 Claahsen, Hedi P1-167
 Claahsen-Van Der Grinten, Hedi T8
 ClaeysSENS, Segolene P1-150
 Clark, AJL RFC13.5
 Clayton, Peter FC12.4, FC12.5, FC12.6
 Clemente, Marisa P1-314
 Clemente, María P2-164
 Clément, Florencia FC14.1, P1-359
 Coban Akdemir, Zeynep P1-273
 Coban, Fatma P1-237
 Cocca, Alessandra P3-270, P3-327
 Coeli-Lacchini, Fernanda RFC13.4
 Coert, Misty P1-388
 Coğulu, Özgür RFC6.4
 Cokkinos, Dennis P2-213, P2-58
 Colak, Berat P2-288
 Colakoglu Er, Hale LB-28
 Colao, Annamaria FC2.3, P1-23
 Colclough, Kevin FC9.2
 Cole, Michael FC5.1
 Colita, Anca P1-202
 Collado-Valiente, Rosa P2-23
 Collignon, Patrick P3-269
 Collings, Sunny P1-279
 Collingwood, Catherine P1-246
 Colombi, Carolina P2-90
 Colombi, Lia P2-167
 Colucci, Silvia Concetta RFC6.2
 Combet, Emilie FC9.5
 Comegna, Laura P3-314
 Comert, Serdar P2-51
 Comertpay, Gamze P1-117
 Cominato, Louise P1-199, P1-39
 Constantacos, Cathrine P1-25
 Contrò, Gianluca P1-194, P2-181
 Convertino, Alessio RFC6.2
 Conway, Gerald FC10.3
 Conwell, Louise P1-64, P1-65, P2-151
 Cooke, Brian P1-158, P1-7
 Cools, Martine MTE1, P1-10, P1-157, P1-167, P1-171, P1-261, P1-271, P2-105, P2-154, RFC3.1, RFC8.6
 Coomans, Ilse P2-105
 Coors, Detlef P3-258
 Corbetta, Carlo P1-423
 Corbetta, Sabrina P1-97
 Corica, Domenico P1-346, P1-422, P1-53, P3-10, P3-209, P3-232
 Cormier-Daire, Valérie P2-176
 Correa Costa, Eduardo P1-167, RFC10.1
 Corredor-Andres, Beatriz P2-239
 Corrias, Andrea RFC5.1
 Corripio, Raquel FC15.5, P1-382
 Corsello, Giovanni P1-392, P1-95, P2-192
 Corvalan, Camila P1-399
 Cosentini, Dora P3-244
 Cossettini, Micol P3-295
 Costa, Carla LB-16, P2-14, P2-4, P3-315
 Costa, Eduardo P1-10, P1-157, P1-270
 Costa, Elaine Maria Fraude P1-270, P3-219
 Costa, Margherita P1-378, P2-182
 Costanzo, Mariana P1-129, P2-259
 Cottrell, Emily P3-167, RFC14.4
 Couper, Jennifer P1-190
 Couto, Yolanda P1-382
 Cox, Kathyrn P1-266
 Craen, Marghareta P2-154
 Creț, Victoria P3-109
 Crinò, Antonino RFC6.2
 Cripps, Amy P1-9
 Cristina Patricia, Dumitrescu P3-114
 Crocco, Marco RFC2.4, T3
 Crosnier, Anne-Sophie LB-11

- Crowley, William F. FC15.1
 Crowne, Elizabeth P1-123, P1-6, RFC13.2
 Crowne, Elizabeth C P2-253
 Crudo, David P1-25
 Cruz, Patricia Sales Marques P3-219
 Cuccaro, Rieko T P1-262
 Culen, Caroline P2-187
 Cunha, Damiana P2-196
 Cunliffe, Vincent T FC10.1, FC15.3
 Curatola, Selenia P1-346
 Cutfield, Wayne FC7.4
 Cutri, Maria Rosa P2-8
- D**
- D'Acunzo, Ida P1-422, P2-287
 D'Apromont, Ivonne P2-46
 D'Hauwers, Kathleen P1-269
 D'Isanto, Livio P2-138
 da Cruz, Aparecido Divino P2-196
 Dabaghao, Preeti P1-280
 Dacou-Voutetakis, Catherine P1-154
 Dadivson, Brenda P1-240
 Daems, Caroline T9
 Dagdeviren Cakir, Aydilek P2-5
 Dagdeviren Cakir, Aydilek P2-137
 Daggag, Hinda P2-112
 Dahlgren, Jovanna P1-195, RFC11.4
 Dalili, Setila P3-111
 Dalili, Setila P3-72
 Dall'Agnese, Angélica P3-35, P3-40
 Damen, Layla FC12.3, FC14.6, P3-178
 Damholt, Birgitte B P1-363
 Damiani, Durval P1-199, P1-39
 Daniel, Eleni P1-167
 Danilenko, Oleg RFC5.3
 Dankovcikova, Adriana P2-168
 Danne, Thomas RFC3.1
 Danyte, Evalda P2-70
 Daousi, Christina P1-102, RFC11.1
 Daraki, Vasiliki P3-192
 Darcan, Şükran P1-414, P3-217, RFC6.4
 Darendeliler, F Feyza P1-262
 Darendeliler, Feyza P1-10, P1-134,
 P1-145, P1-157, P1-159, P1-167,
 P1-236, P1-306, P1-390, P2-195,
 P2-270, P2-45, RFC10.1
 Daroszewski, Jacek RFC12.2
 Darvish, Elsa P1-257
 Das, Urmi P1-102, P1-167, P2-190
 Dasgupta, Kaberi P1-318
 Dasheva, Anna P3-256
 Dashkevich, Helena P2-111
 Dastamani, Antonia P1-205, P2-143,
 P3-266, RFC9.4, RFC9.5
 Datar, Chaitanya P3-162
 Dateki, Sumito FC3.4, P1-170
 Dattani, Mehul FC11.2, P1-120, P1-6,
 RFC13.2, RFC3.1, RFC5.4
 Dattani, Mehul T FC11.1
 Daubenbüchel, Anna M. P1-99
- Dave, Chetan P2-73, P3-227
 David, Alessia FC8.5
 Davidse, Kirsten FC8.3
 Davies, Janene P2-151
 Davies, Justin H P1-6, RFC13.2
 Davies, Stephen P1-158, P1-7
 Davis, Elizabeth P1-35
 De Angelis, Gian Luigi P2-150, P3-133
 De Angelis, Simona P1-423
 de Araújo, Iana Manuelle P1-199
 De Bellis, Annamaria T3
 De Boissieu, Paul P1-213
 de Bruin, Jan Peter LB-12
 de Castro, Simone Martins P1-155
 de Catro, Margaret RFC13.4
 De Dios, Olaya P3-99
 De Filippis, Tiziana P1-420
 de Fluiter, Kirsten P2-126
 de Fluiter, Kirsten S P1-52
 De Franco, Elisa P1-27, P2-90, P2-99
 de Goede, Paul FC13.4
 de Graaff, Laura FC12.3, FC8.3
 de Graaff, Laura C.G. P1-367
 de Kruijff, Ineke RFC13.3
 de la Torre, Marina P2-61
 de Lamas, Carmela P3-119
 De Leon, Mary Rosalynn FC4.6
 De Lonlay, Pascale LB-11
 De Luca, Filippo P1-422
 De Masi, Salvatore P1-107
 De Mori, Letizia RFC12.5
 de Muinck Keizer-Schrama,
 Sabine RFC2.5
 de Rijke, Yolanda RFC13.3
 de Rijke, Yolanda B. P1-158, P1-7
 de Roux, Nicolas P2-251
 De Roux, Nicolas RFC15.6
 de Sanctis, Luisa P2-208, P3-30
 De Sanctis, Luisa P1-20, P1-400, P1-422,
 RFC11.2
 De Sanctis, Vincenzo P3-185
 De Schepper, Jean P2-153, P2-154
 De Silva, Dimarsha P3-291, P3-321
 De Silva, Dimarsha P3-322
 De Silva, Shamyia P3-271
 De Silva, Varuni P3-271
 De Silvestri, Annalisa P1-323, P3-115,
 P3-98
 De Simone, Luciano P2-21
 de Truchis, Camille P1-18
 de Vos, Willem T15
 de Vrie, Liat P1-10
 de Vries, Annelou S6.2
 de Vries, Liat P1-109, P1-157, P1-167,
 P1-187, P1-291, RFC10.1, T17
 de Vries, Martine P2-257
 De Waele, Kathleen P1-171, P2-105
 de Zegher, Francis FC4.3, FC9.3, P1-193,
 P3-120, RFC4.3, T1
 De, Hriday P2-113, P3-57
- Deboni, Mariana P1-199
 Debza, Yahya FC6.6
 Deeb, Asma P3-183
 Deehan, Edward P1-49
 DeFranco, Elisa P1-207
 Dehayem, Mesmin P3-125
 Dekkers, Olaf RFC3.1
 Del Pozo, Angela RFC1.4
 Del Valle Rossi, Romina P3-107
 del-Río-Navarro, Blanca Estela P1-43
 Deladoëy, Johnny FC5.4, P1-425
 Delaney, Angela FC15.1
 Delcour, Clémence RFC15.6
 Della Casa, Elisa RFC9.6
 Della Latta, Veronica P1-260, P1-58
 Delopoulos, Anastasios P3-101
 Delvecchio, Maurizio P2-171
 Demdoum, Mohamed P1-296
 Demet Akbas, Emine P3-22, P3-259
 Demet Akbaş, Emine P1-103, P1-351,
 P2-44
 Demir, Berrin P1-241
 Demir, Hulya P1-239
 Demir, Korcan P1-28, P2-284, P3-198,
 P3-250
 Demiral, Meliha P1-91, P1-207, P1-254
 Demirbas, Ozgecan P1-329
 Demirkilek, Huseyin P1-207, P1-254,
 P1-71
 Demirkilek, Hüseyin P1-91
 Demirci, Gulsah P2-119
 Demirci, Gülsah P1-160, P3-225
 Demirci, Tuba LB-2, LB-6
 Demirhan, Salih P1-48
 Demirtaş, Tuna FC7.5
 Demir, Korcan P1-285
 Dennig, Michelle P1-309
 Denvir, Loiuse P3-155
 Denvir, Louise P1-352, P1-384
 Denyer, Hayley P1-375
 Denzer, Christian RFC11.5, RFC7.2
 Denzer, Friederike P1-262
 Deodati, Annalisa FC7.3, P1-14, P1-260,
 P1-386, P1-58
 Derazne, Estela P2-123
 Derkaoui, Nada P3-240
 Derkaoui, Nada P3-86
 Dermitzaki, Eleni P1-16, P3-301
 Derraik, José FC7.4, P1-50, P2-121
 Derraik, José G B LB-24
 Deshpande, Ruma P2-108, P2-152,
 P3-104
 Deshpande, Tushar P3-171
 Desideri, Elena P3-17
 Detho, Nina P1-132
 Dewantoro, Dickson RFC2.6
 Dewulf, Charline P2-154
 deZegher, Francis P1-56, P2-127
 Dharmaraj, Poonam P2-190
 Dharmraj, Poonam P1-102

- Dhooge, Catharina P1-171, P2-105
 Di Carlo, Silvia P1-300
 Di Frenna, Marianna P1-420, P1-423, P2-298
 Di Giovanni, Fabiana P1-194, P2-181
 Di Grazia, Massimo P3-244
 Di Iorgi, Natasca P1-251, P1-252, P1-391, P1-97, RFC11.2, RFC12.5, RFC2.4, T3
 Di Mase, Raffaella P1-401, P1-409, P2-287
 Di Natale, Valeria P2-92
 Di Palma, Isabel P1-249
 Di Rocco, Federico FC2.3
 Di Sessa, Anna FC4.4, P1-354, P1-45
 Di Somma, Carolina FC2.3, P1-23
 Diamantino, Catarina LB-16, P3-315
 Diankova, Diana P1-307
 Dias, Sara P1-253
 Diaz, Lorena P3-186
 Diaz-Escobar, Laura A P3-286
 Didi, Mohammed FC9.2, P1-102, P1-259, P2-180, P2-190, P2-236
 Dieguez, Carlos P1-345
 Diene, Gwenaelle P1-139
 Dies Suárez, Pilar RFC1.3
 Dies, Pilar P1-15
 Dietrich, Arne FC4.2
 Diez-Lopez, Ignacio P3-316, P3-320, P3-333
 Digweed, Dena P1-156
 Dikaiakou, Eirini P3-102
 Dikaiakou, Eirni P3-126
 Dilek, Semine RFC15.2
 Dimitriadou, Meropi P1-166
 Dimitrova-Dasheva, Anna P1-307
 Dimitrova-Mladenova, Mihaela P3-108, P3-256
 Ding, Yu P1-277, P2-188, T20
 Diniz Faria Júnior, José Antônio P1-135
 Diou, Christos P3-101
 Direk, Gül P1-244, P3-134, P3-263
 Dirlewanger, Mirjam P2-264
 DiRocco, Federico P2-226
 Diver, Louise A RFC10.3
 Direk, Gül P2-169, P3-67
 Djermane, Adel P3-113
 Do Thanh, Mai P3-21, P3-260
 Do, Thi Thanh Mai P2-7
 Dobbiani, Giulia P2-64, P3-115
 Dobreńko, Elżbieta P2-36
 Dobrovolskiene, Rimante P2-70
 Dogan, Beyza Belde P1-283
 Dokucu, Ali İhsan P2-255
 Dolan, Conor FC13.2
 Dolman, Koert FC13.4
 Domenice, Sorahia P1-135, P1-262, P1-270, P3-219
 Dominguez Riscart, Jesus P1-374
 Dominguez, Gonzalo P2-46
 Dominguez, Jesús P2-145, RFC1.4
 Domouzoglou, Eleni P1-54
 Domènec Mercadé, Ivan FC10.2
 Donaghue, Kim S4.2
 Donaldson, Malcolm P3-196
 Donaldson, Malcolm FC5.1, FC9.5, P2-2
 Dondup, Olga P2-245, P3-242
 Doneray, Hakan P3-235, P3-61
 Dong, Guanpin P2-27
 Dong, Guanping LB-24, P1-200, P2-121, P2-29, RFC4.2
 Dong, Lijin RFC15.5
 Dong, Zhiya P2-81, P3-204, P3-261
 Donner, Birgit P1-29
 Donner, Julia FC6.5
 Donze, Stephany FC12.3, FC14.6, FC8.3, P1-367, P3-178
 Doodson, Louise P2-143
 Dorado-Ceballos, Estefanía P1-193
 Dorst, Kristien RFC13.3
 Dos Santos, Tiago Jerónimo P2-239
 Dosa, Laura P1-194, P1-336
 Dost, Axel FC7.6
 Doulgeraki, Artemis P3-275
 Doyle, Robert P. RFC4.6
 Doz, François P2-226
 Doğan, Ozlem FC6.4
 Drakoulis, Nikolaos P2-140
 Drapeau, Vicky P1-197, P1-57
 Dreifuss, Amatzia RFC10.6
 Dreyer, Kim LB-12
 Drimtzias, Evangelos RFC11.1
 Drira, Leila RFC15.6
 Driul, Daniela P1-106, P1-401, P2-232
 Drop, Stenvert SS1.2
 Drosatou, Chrysoula P1-96
 Du Bois, Philipp FC15.2
 Du, Caiqi RFC1.5
 Du, Minlian P2-114, P3-193, P3-222
 Du, Minlian P3-6
 Du, Minlian P3-241, P3-44
 Du, Minlian P3-151
 Dube, Juan De Dios P1-331
 Duffert, Christin P1-365, P2-269
 Dufour, Christelle P2-226
 Duijnhouwer, Anthonie P1-388
 Dujovne, Noelia LB-26
 Dumant-Forrest, Clémentine LB-4
 Dumic Kubat, Katja P2-10, P2-179
 Dundar, Munis P2-5
 Dunger, David FC5.1
 Dunger, David B. RFC14.5
 Dunkel, Leo FC15.4, FC8.5
 Dura, Teodoro P2-277
 Durante, Viviana P1-417
 Durmus Kaygısız, Merve LB-2
 Durá-Travé, Teodoro P3-116
 Dusatkova, Petra FC12.2
 Dwivedi, Gaurav RFC10.4
 Dzięcioł, Janusz T2
 Díaz, Francisca FC8.2, FC8.4
 Díaz, Marta FC4.3, T1
 Díez, Ignacio P2-279
 Döbeln, Viola P1-42
 Dötsch, Jörg P1-42
 Döger, Esra P1-103, P1-351, P2-103, P2-44, P3-56
 Dündar, Bumin P1-308, P1-321, P3-215
 Dündar, Bumin Nuri P1-143, P1-245, P1-335, P3-106, P3-159, P3-182, P3-226
- E**
 E. Silva, Tatiane P1-135
 Eardley, Sue P1-327
 Easter, Shelley P2-108, P3-104
 Eberle, Birgit FC5.5
 Ebidy, Mai P2-120
 Echeverría, Gimena P2-297
 Edan, Anne P2-264
 Edouard, Thomas P1-139, P1-150
 Edouard, Thomas P3-33
 Efthymiou, Vasiliki P3-275, P3-302
 Egerbacher, Monika FC6.2
 Ehehalt, Stefan P1-51
 Ehlayel, Mohammad P3-28
 Ehtisham, Sarah P3-183, RFC7.1
 Eide, Geir Egil P1-110, P1-258
 Eideh, Hasan P3-45
 Einaudi, Silvia P1-10, P1-167, P1-300
 Eker, Nursah P2-25
 Ekinci, Deniz P1-294
 Ekström, Klas P2-162
 El Allali, Yasmine T8
 El Arbi, Kawthar P3-216
 El Bardeny, Magdy P2-258
 El Bejjani, Mireille P2-17
 El Gammal, Mona P2-256
 El Neily, Dalia P3-78
 El Sharkawy, Sonia P3-94
 El-Eshmawi, Ahmed P3-140
 El-Hawary, Amany P3-140
 El-hawary, Amany P3-77
 El-Helaly, Rania P3-77
 El-Rifai, Omar P1-211
 Elabany, Ahmed P2-120
 Eladely, Gehad P2-120
 Elalaily, Rania P3-138
 Elawwa, Ahmed P2-11, P2-43, P2-50, P3-138, P3-139, P3-183, P3-74
 Elbarbary, Nancy P1-180, RFC1.6
 Elblova, Lenka FC12.2, RFC14.2, RFC6.6
 Elcioglu, H.Nursel P2-52
 Elechi, Hassan Abdullahi P1-384, P3-155
 Elena, Kiseleva P3-224
 Elfers, Clinton FC4.6
 Elfers, Clinton T. RFC4.6
 Elfving, Maria P1-419
 Elgebaly, Asmaa P3-90
 Elgharbawy, Fawzia P3-152

- Elias, Lucila RFC13.4
 Elias-Assad, Gadhir P1-430
 Elias-Assad, Ghadir P2-244
 Elizabeth, Melitza P1-367
 Eljaszewicz, Andrzej FC5.2
 Elkun-Tamir, Erella P1-265, P2-6
 Ellard, Sian P1-207, P1-27, P2-149, RFC9.4
 Elli Francesca, Marta P2-48
 Elmaogullari, Selin P1-255
 Elmaogullari, Selin P3-180
 ELMougy, Fatma LB-8
 Elowe-Gruau, Eglantine P1-424
 Elsayed Abdel Meguid Ahmed, Shayma P2-11
 Elsayed, Nagwa P2-183
 Elsayed, Shaymaa P1-413, P2-258, P2-33
 Elsedfy, Heba P1-10, P1-157, P1-167
 Elsharkasi, Huda M. FC2.5
 ELShennawy, Hala LB-8
 Elsiddig, sohair P2-193
 Elsiddig, Sohair P2-156, P3-28
 Elsiddig, Suhair P1-381
 Eltan, Mehmet P1-175, P1-176, P1-273, P2-25, P2-52, P3-202, P3-80
 Eltan, Mehmet P1-3, P1-402
 Elvira, Kasatkina P3-224
 Emara, Doaa Mokhtar P2-50
 Emodi, Ifeoma P2-199
 Empting, Susann FC9.6
 Endo, Takaaki LB-1
 Engin, Muhammet Mesut Nezir P3-62
 Eozenou, Caroline FC10.3, P1-127
 Er, Eren P1-414
 Er, Hale P1-112
 Er, Hale Colakoglu RFC8.1
 Erbaş, İbrahim Mert P1-28, P3-198, P3-250
 Ercan, Oya P2-137, P2-5
 Erdeve, Şenay Savaş P1-160, P3-225, P3-9
 Erdogan, Kadri Murat P3-19
 Eremcic, Rodica P1-108
 Eren, Erdal P1-329
 Eren, Funda P2-255
 Erfurth, Eva-Marie P1-419
 Ergelen, Rabia P2-25
 Ergin, Malik P3-233
 Ergül Türel, Ayça P2-137
 Ernoult, Perrine T8
 Eroğlu Filibeli, Berna P1-143, P1-245, P1-308, P1-321, P3-106, P3-159, P3-182, P3-215, P3-226
 Ersoy, Betül P3-285
 Ertl, Diana- Alexandra P1-76
 Ertl, Diana-Alexandra P2-187
 Escobar, María Eugenia LB-7
 Escosa Garcia, Luis P1-374
 Escribano Subias, Joaquin P3-293
 Escribano, Arantxa RFC1.4
 Esmailzadehha, Neda P1-24
 Espada, Filipa P1-253
 Espinosa-Espíndola, Montserrat P1-15
 Esposito, Andrea P2-287
 Essaddam, Leïla P2-77, P3-238
 Essawi, Mona P3-230
 Etani, Yuri P2-170
 Evangeliou, Athanasios P2-301
 Evangelopoulou, Cathrine P1-432
 Evciler, Hüseyin P3-233
 Eveslage, Maria P1-398, P1-99
 Evliyaoglu, Olcay P2-5
 Evliyaoğlu, Olcay P2-137
 Evsyukova, Evgeniya P3-253
 Eyal, Ori P1-397, P2-1
 Ezzati Mobasser, Samira FC4.1
 Ezzerouqi, Amine P3-86
 Ezzerouqi, Amine P2-274
- F**
- Fabretto, Antonella LB-22
 Fabris, Bruno LB-18
 Fabris, Francesco P3-295
 Faccioli Bodoni, Aline RFC13.4
 Faienza, Maria Felicia P1-300, P1-422, P2-171, P3-232, RFC6.2
 Fakhry, Antoine LB-8
 Faldum, Andreas P1-398
 Faleschini, Elena LB-18
 Falhammar, Henrik P1-299
 Fan, Lijun P1-263
 Fang, Yanlan FC1.1, P1-297, P3-223
 Fanis, Pavlos P1-334, P1-394, P2-275, RFC8.3
 Fanolla, Antonio P3-267
 Fantini, Jacopo P1-401, P2-232
 Fardella, Carlos P1-338
 Farndon, Sarah RFC11.1
 Farzamfard, Venus P3-72
 Fasano, Victoria P1-8
 Fattal-Valevski, Aviva P1-347
 Fatti, Letizia Maria P1-120
 Faust, Kelly P2-136
 Fava, Daniela P1-251, P1-252
 Fawzy, Dina P3-143
 Fawzy, Dina P3-90
 Fdhila, Faten P2-77
 Feil, Patricia FC2.4
 Fejzic, Zina P1-388
 Feldman Witchel, Selma P1-142
 Felici, Francesca RFC3.5
 Felipe, Laura LB-26
 Feliu Rovira, Albert P3-293
 Ferenczova, Juliana P2-168
 Fernandez, Maria Celia FC14.1
 Fernandez-Quintela, Alfredo P3-320
 Fernando, Jerard P3-322
 Fernane, Leila P3-176, P3-201
 Fernández González, Lucía P1-272
 Fernández Mentaberry, Verónica P2-228
 Fernández, María Celia P1-359
- Fernández, María Concepción P2-279
 Ferrari, Fabrizio P1-68, RFC9.6
 Ferrari, Maria Tereza Martins P1-270, P3-219
 Ferrari, Vittorio P1-107
 Ferreira, Cristina P3-157
 Fessatou, Smaragdi P2-40
 Fessatou, Smaragdi P2-214
 Festa, Adalgisa P1-93
 Festa, Adalgisa P1-111
 Fica, Simona P1-202
 Fichna, Piotr P1-287
 Fideleff, Hugo P3-283
 Fielitz, Jens FC15.2
 Filatova, Natalia P2-221
 Filho, Guilherme P1-157
 Filioussi, Fotini P3-301
 Filippova, Tatiyana P1-328
 Filis, Konstantinos P3-101
 Fink, Katharina FC7.6
 Finken, Martijn FC13.2, LB-12, P1-167
 Finken, Martijn J.J. FC13.4
 Finken, Martijn JJ P1-10
 Fintini, Danilo P1-14, P2-232, RFC6.2
 Fisch Shvalb, Naama P2-267
 Fitouri, Zohra P2-77
 Flanagan, Sarah FC9.2, P1-64, P1-65, RFC9.4, S8.2
 Flanagan, Sarah E P1-207
 Flanagan, Sarah E. P2-149, RFC9.5
 Flechtner, Isabelle P1-80
 Fleischer, Kathrin P1-269, P1-377, RFC12.1
 Fletcher, Suzanne FC9.5
 Fliers, E. RFC9.2
 Flitsch, Jörg P1-398
 Flores, Adriana P1-240
 Flores, Mónica P1-274
 Floroskoufi, Paraskevi P3-192
 Flot, Claire P1-150
 Flueck, Christa RFC10.1
 Flueck, Christa E. P1-281, RFC15.3
 Flury, Monika P2-205
 Flück, Christa P1-164
 Flück, Christa E P2-3
 Flück, Christa E. P1-309
 Flück, Christa Emma P3-83
 Folgueira, Cintia P1-345
 Fomenky Njiandock, Cecilia P3-125, P3-137
 Fonseca, Marcelo LB-16, P3-315
 Fontoura, Manuel P2-14, P2-4
 Forget, Patricia P3-194
 Forgetta, Vince RFC6.3
 Formicola, Daniela P1-194, P1-336, P1-362, P2-181
 Fornells Albanell, Eduard P3-107
 Forsander, Gun P1-22
 Forysth, Vhari RFC11.3
 Forzano, Giulia P1-194, P2-181

- Foster, John E. FC2.5
 Fotinou, Aspasia P1-432, P2-251, P3-102, P3-126
 Foukas, Periklis P2-214
 Foulkes, William D RFC5.2
 Fox, Krystal P2-231
 Frago, Laura FC8.2, FC8.4
 Frago, Laura M. FC15.6
 Fraissinet, François LB-4
 Franch, Noemi P1-382
 Franchioni, Liliana P1-364
 Franco, Francesca P2-232
 Francuz, Tomasz P1-373
 Franik, Sebastian P1-269
 Frank, Leonie P1-210
 França, Monica P1-291
 Fratzl-Zelman, Nadja FC6.1, RFC15.5
 Frederiksen, Hanne P1-136, T4
 Frei, Jennifer P1-318
 Freijo Martin, Concepcion P2-74
 Freijo Martin, Concepción P2-102
 Freire, Analía Verónica LB-7, P1-72
 Freire-Regatillo, Alejandra FC8.2, FC8.4
 Freitas, Joana LB-16, P3-315
 Freriks, Kim RFC2.5
 Fresneau, Brice P2-226
 Fresneau, Laurence P2-176
 Friedrich, Clemens P1-301
 Frixou, Maria P1-334
 Froehlich-Reiterer, Elke HDI2.3, P2-187
 Frolova, Elena P2-250
 Frumkin Ben-David, Rachel RFC7.5
 Frystyk, Jan RFC14.5
 Fröhler, Sebastian FC15.2
 Fu, Lijun T20
 Fu, JunFen LB-24
 Fu, Junfen RFC4.1
 Fu, Junfen P1-200, P2-121, P2-29, RFC4.2
 Fudvoye, Julie P3-254
 Fuery, Michelle P2-151
 Fujisawa, Yasuko T16
 Fujisawa, Yusuke P1-406
 Fujiwara, Ikuma P1-115, P2-285, P3-27
 Fujiwara, Makoto P1-168
 Fukami, Maki FC3.1, P1-140, RFC1.1, RFC12.3, T16
 Fuke, Tomoko RFC12.3
 Funari, Mariana P1-135
 Funda, David P. P2-69
 Furdela, Viktoriya P2-299
 Furmaniak, Jadwiga P2-293, P2-36
 Furtak, Aleksandra P3-280, P3-288
 Fylaktou, Irene P1-118
 Förtsch, Katharina P2-20
- G**
 Gabau, Elisabeth P1-382
 Gabbay, Uri LB-5
 Gad, Suzan P3-309
- Gaeta, Giuliana P1-360
 Gaeta, Valeria P1-409
 Gaisl, Odile P2-271, RFC10.5
 Galati, Maria Concetta P2-300
 Galazzi, Elena P1-120
 Galcheva, Sonya P2-149, P2-173, P2-174, T13
 Galhardo, Júlia P2-107
 Galletta, Karol P3-209
 Galli-Tsinopoulou, Assimina FC7.1, P2-301
 Gallizia, Annalisa P1-251, RFC11.2, RFC2.4, T3
 Gallo, Dario P2-232, P3-144, P3-205
 Gallo, Francesco P3-287
 Galluzzo Mutti, Maria laura P2-259
 Galo, Elisa P1-253
 Gamal Heiba, Ebtehal P3-309
 Gamble, Ashley RFC11.1
 Gan, Hoong-Wei RFC11.1
 Gangoda Liyanage, Dilusha P3-271
 Gannouni, Souha P1-26, P3-196
 Gantz, Marie P1-49
 Gao, Kang P3-324
 Garavelli, Lidia P3-133
 Garcia Cuartero, Beatriz P2-128
 Garcia Lacalle, Concepcion P2-128
 Garcia Lombardi, Mercedes FC14.1
 Garcia, Hernan P1-37, P2-46
 Garcia, Hernan Jorge P1-37
 Garcia, Maria Dolores P2-277
 Garcia, Marie Isabelle FC8.5
 Garcia, Rosa Maria Rahmi P1-155
 Garcia-Beltran, Cristina P3-120
 Garcés, Carmen P3-99
 Garcia Lombardi, Mercedes P1-359
 García, Hernán P1-338
 García-Palacios, María P1-345
 García-Rivera, Sonika FC15.5
 Gardner, Melissa P1-125
 Gardstedt, Jenni P1-119
 Gargouri, Imen P1-94, P2-39, P3-170, P3-229, P3-252, P3-97
 Gargouri, Imene P2-266, P3-216, P3-221, P3-25
 Garibay-Nieto, Nayely P3-286
 Garner, Terence FC12.4, FC12.5, FC12.6
 Garré, Maria Luisa RFC2.4, T3
 Garten, Antje P1-30, RFC4.4
 Garzón, Lucía RFC1.4
 Gasowska, Marta p1-421
 Gasperikova, Daniela P2-91
 Gastaldelli, Amalia P1-260, P1-58
 Gastaldi, Roberto P1-252
 Gat-Yablonski, Galia P1-109
 Gaudino, Rossella P1-5, P1-97
 Gaudino, Rossella RFC9.3
 Gavela-Pérez, Teresa P2-23, P3-99
 Gavrilova, Anna P2-109
 Gawlik, Aneta P1-373, P1-53
- Gazek, Natalia LB-26
 Gebenlian, Juliana RFC13.4
 Gelander, Lars P1-59, RFC12.6
 Gencay, Ali Genco P1-236
 Genitori, Lorenzo P1-401
 Georgantzi, Maria P2-214
 George Paul, Praveen P1-169
 George, Biju P1-169
 Georgieva, Raliza P1-307
 Gerali, Maria P1-96
 Gerasimidis, Konstantinos RFC2.6
 Geremia, César P3-35, P3-40
 Gerges, Mary FC4.5
 Gerlitz, Offer RFC10.6
 German, Alina P1-59
 Geronikolou, Styliani P1-242, P2-204, P2-213, P2-58
 Gesing, Julia P2-110
 Gevers, Evelien P1-6, RFC13.2
 Gevorgyan, Nune P2-96
 Geyer, Armin FC13.1
 Gezdirici, Alper P1-248
 Ghergherehchi, Robabeh P2-47
 Ghorbel, Dorra P3-170, P3-97
 Ghosh, Sujoy P1-276
 Ghubatyan, Anna P2-96
 Giabicani, Eloise P1-303
 Giabicani, Eloise P1-218
 Giabicani, Eloïse FC12.1
 Giaccaglia, Silvia P1-240
 Giacobini, Paolo S11.2
 Giacomozzi, Claudio P2-171, P3-277
 Gianetttoni, Jill P1-235, P1-84
 Giannini, Cosimo LB-13, P3-274, P3-314
 Giannopoulos, Andreas P3-184, P3-53
 Gianti, Francesca P1-251
 Giatropoulou, Sofia P2-66, P3-4
 Gibertoni, Dino P1-378
 Gieburowska, Joanna P1-373
 Giemza, Tomasz P1-387, P1-87
 Gies, Inge P2-154
 Giglio, Sabrina P1-194, P1-336, P1-362, P2-181
 Gil, Silvia P1-249
 Gil, Ángel P1-33, P1-345, P3-119
 Gil-Barcenilla, Begoña P2-118
 Gil-Campos, Mercedes P1-33, P1-345, P3-119
 Gil-Poch, Estela P3-306
 Gilbert, Clare P1-205
 Gilbert, Clare RFC9.4, RFC9.5
 Gilbey-Cross, Robyn P3-270
 Gilkes, Catherine P1-102
 Gillespie, Kathleen M. FC1.5
 Gilligan, Lorna C. P1-162
 Gillis, David P2-146, P3-16
 Giorgadze, Elene FC14.4
 Girgis, Rose P1-427, P2-34
 Girgis, Safwat P1-427

- Giri, Dinesh P2-108, P2-152, P2-260, P3-104
 Giugno, Andrea P2-75
 Giunti, Laura P1-194, P1-336
 Giwercman, Aleksander P1-419
 Giza, Styliani FC7.1, P2-301
 Gjikopulli, Agim P3-175
 Gjurkova-Angelovska, Beti P3-284
 Glaser, Ben P3-281
 Gleiss, Andreas FC6.2
 Globa, Eugenia P2-281, P3-237
 Globa, Evgenia FC10.3, FC10.4, P1-127
 Globa, Evgeniya P2-272
 Glorieux, Francis RFC2.1
 Goar, Okminyan P3-224
 Goddijn, Mariette LB-12
 Godefroy, Alice P3-269
 Godinho, Adriana P3-35, P3-40
 Goedegebuure, Wesley P1-366
 Goff, Nicole RFC5.4
 Goffin, Sarah FC7.4
 Gofman, Fedor P2-35
 Gohlke, Bettina FC9.4, P1-234
 Gokceoglu, Ayris P1-255
 Golovan, Andrey FC11.5
 Goldstein, BatEl LB-5
 Golli, Tanja RFC3.6
 Golmayo, Luz P3-276
 Gomes, Maria Miguel P3-318
 Gomes, Nathalia Lisboa P1-270, P3-219
 Gomez-Palomeque, Juan Antonio P1-331
 Gomez-Vilarrubla, Ariadna FC9.3
 Gonc, E. Nazli P1-404, P2-223, P2-224
 Gonchar, Margaryta P2-106
 Gonen, Z. Burçin FC11.2
 Gong, Chun-xiu P3-145
 Gong, Chunxiu P2-222
 Gong, Chunxiu P1-263, P1-316, P2-177, P3-154, P3-218, P3-60
 Gong, ChunXiu P1-76, P2-121
 Gong, Maolian FC15.2
 Gonzalez Casado, Isabel P1-374
 Gonzalez Ramos, Javier P1-249
 Gonzalez Vergaz, Amparo P2-128
 Gonzalez, Isabel RFC1.4
 Gonzalez, Javiera P1-240
 Gonzalez, Laura P3-238
 Gonzalez, Veronica P1-8
 González, Isabel P2-145
 González-Briceño, Laura G. P2-226
 González-Leal, Rocío P2-129
 González-Saenz, Patricia P1-345
 Goralczyk, Aleksandra P1-293
 Gordzeladze, Marine P1-151
 Gorelyshev, Alexander FC11.4
 Gorelyshev, Sergey FC11.4, FC11.5
 Gotta, Verena FC7.2
 Gottlieb, Silvia P1-410
 Gozzi, Tiziana P3-84
 Grabowski, Thomas FC4.6
 Graf, Stefanie P1-281, P2-3
 Graham, Peter P1-158, P1-7
 Granata, Francesca P3-209
 Grandone, Anna P1-111, P1-300, P1-401, P2-171, RFC11.2
 Grandone, Anna P1-93
 Grano, Maria RFC6.2
 Grant, Cameron P1-50
 Grant, Vincent P1-9
 Graph-Barel, Chana RFC7.5
 Grapin, Mathilde P1-18
 Grau, Gema P2-254, P2-279
 Gravholt, Claus H. MTE 3
 Gray, Ewan P2-2
 Graziano, Sara FC3.2
 Grazzani, Livia P2-8
 Greaves, Ronda P1-158, P1-7
 Greco, Marco P2-21
 Greenfield, Andy FC10.3, S3.3
 Gregory, Louise FC11.2
 Gregory, Louise C FC11.1
 Grigolato, Anabella P3-107
 Grill, Jacques P2-226
 Grimbley, Chelsey P2-34, P3-234
 Grineva, Elena P1-256
 Grinspon, Romina P. P1-410
 Grinspon, Romina Paula LB-7
 Grisuk, Ivan P2-172
 Groessl, Michael P1-164
 Groom, Katie FC7.4
 Grootjen, Lionne P3-178
 Gross, Scott RFC13.1
 Grossi, Armando P1-14, P2-232
 Grossman, Ehud P2-123
 Group, GOSeqene FC11.2
 Groussolles, Marion P3-33
 Groß, Maximilian P2-144
 Grubczak, Kamil FC5.2
 Gruber, Noah FC1.6, LB-25, RFC5.5, RFC7.5
 Gruenewald, Mathias FC9.4
 Grugni, Graziano P3-267, RFC6.2
 Grunenwald, Solange P1-269, T8
 Gruszczyńska, Katarzyna P1-53
 Gryngarten, Mirta Graciela LB-7
 Gryparis, Alexandros P1-154
 Grywalska, Ewelina T5
 Gu, Yi P3-60
 Guadilla, M. Luisa P2-254
 Guaragna-Filho, Guilherme P1-167
 Guarducci, Silvia P1-194, P1-336, P2-181
 Guarino, Stefano P1-45
 Guasti, Leonardo FC15.4, FC8.5, S7.1
 Guazzarotti, Laura LB-22, P1-300, P1-418
 Gubaeva, Diliara P1-206, RFC9.5
 Gubayeva, Dilyara P1-69
 Gucev, Zoran P1-149, P2-216
 Gue, Sam P1-190
 Guedri, Rahma P3-238
 Guedria, Asma P3-93
 Guercio Nuzio, Salvatore P2-138
 Guercio, Gabriela P1-129, P2-259
 Guerra-Cantera, Santiago FC8.2, FC8.4
 Guerra-Júnior, Gil P1-85
 Guerrero, Julio RFC1.4
 Guerrini-Rousseau, Léa P2-226
 Guerrot, Anne-Marie LB-4
 Guilmin-Crepion, Sophie RFC3.2
 Guizzardi, Fabiana P1-420
 Gullu, Ufuk Utku P1-71
 Gulli, Mariolina FC3.2
 Gulordava, Athina P2-301
 Gulsen, Hayriye P1-239
 Gumeniuk, Olga P2-148, P3-177
 Gunadi, Hartono P3-300
 Gunasekara, Buddhi P3-291, P3-304, P3-321
 Gunasekara, Buddi P2-80, P3-322
 Gunes, Nilay P2-5
 Gunes, Yasemin RFC15.1
 Gunn, Harriet RFC11.3
 Guntsche, Zelmira P2-90
 Guo, Hui FC12.6
 Guo, Song P3-241, P3-44
 Guo, Song P2-114, P3-151, P3-193, P3-222
 Guo, Song P3-6
 Guo, Yan P3-261
 Gurcan, Tulay P1-3, P1-402
 Gurcan, Tulay P1-116
 Gurcan, Tulay P1-10, P1-159, P1-162, P1-167, P1-175, P1-176, P1-273, P1-53, P2-25, P2-52, P3-202, P3-80, RFC10.1
 Gurbuz, Fatih RFC15.2
 Gurpinar Tosun, Busra P1-175, P1-176, P2-52, P3-202
 Gurpinar, Busra P1-402
 Gursoy, Semra P3-124
 Gurturcan, Nursen P1-142
 Gustafsson, Jan P2-162
 Guterman-Ram, Gali FC6.1
 Gutierrez, Carolina P3-276
 Gutierrez, Joaquin P1-418
 Gutierrez, Marcela P1-410
 Guven, Alya RFC10.1
 Guven, Ayla P1-10, P1-157, P1-162, P1-167, P2-262
 Guyers, Mark P2-88
 Guzzetti, Chiara P1-106, P1-401, P2-132, P2-171
 Gärskog, Helena P3-7
 Gómez-Aragón, Isabel P2-23
 Gómez-Neo, Ana P2-23
 Gök, Ebru P3-263
 Gök, Ebru Suman P2-169
 Gökşen, Damla P1-414, P2-137, P3-217, RFC6.4
 Güçüyener, Kivilcım P2-103
 Güemes, Maria P1-376

- Güemes, María P3-276
 Gül Şiraz, Ülkü P3-263
 Güran, Tülay P3-220, P3-3
 Güran, Tülay FC13.5, P1-157, P2-255
 Gürbüz, Fatih P1-411
 Gürkan, Ferda Evin RFC6.4
 Güven, Ayla P1-48, P2-13, P2-53, P3-243
- H**
- H, Fetouh P3-70
 H.A. Kaplan, Emel P2-288
 Ha, Eun-Hee P1-40
 Habeb, Abdelhadi P3-183
 Habeb, Abdulhadi P1-161
 Haberman, Yael LB-25
 Habib, Asadollah P3-249, P3-255
 Habib, Ashkan P3-249, P3-255
 Hachemi, Maouche P1-292, P2-161
 Hachicha, Mongia P1-322, P1-94, P3-170, P3-229
 Hachicha, Mounchia P3-25
 Hachiya, Rumi P1-173
 Hacihamdioglu, Bulent P2-235, P2-51
 Hacohen Solovitz, Amir P2-146
 Haddad, Naima P3-128
 Hadj Kacem, Faten P2-266, P3-206, P3-216, P3-221, P3-25
 Hadj Kacem, Hassen P2-266
 Hadjkacem, Faten P1-94, P2-39, P3-170, P3-229, P3-252, P3-97
 Hadrich, Zouhour P3-93
 Hadziselimovic, Faruk RFC10.2
 Haeusler, Gabriele P1-76
 Haeusler, Gabriele FC2.4, FC6.2, P2-187, RFC15.5
 Hafez, Mona LB-8
 Hagen, Casper P1-114
 Hagen, Casper P FC11.6
 Haklar, Goncagul P1-162
 Haklar, Goncagul P1-3
 Haliloglu, Belma P1-207, P3-118
 Halvadjian, Irina T13
 Halvadzhyan, Irina P2-173
 Hamad, Noor P3-165
 Hamajima, Takashi P1-298
 Hamdi, Safouane P1-139
 Hamdy, Ahmed LB-17
 Hamed, Amira P3-41
 Hamed, Noor P2-43, P3-50, P3-74
 Hamidova, Olha P3-237
 Hamiel, Uri P1-397, P2-123
 Hamilton - Shield, Julian P3-104
 Hamilton - Shield, Julian P. FC1.5
 Hamilton-Shield, Antonia P1-123
 Hamilton-Shield, Julian P2-108
 Hamilçikan, Şahin P1-208
 Han, Heon Seok P3-172
 Hana, Mona P1-34
 Hana, Vaclav P2-281
 Hanmehmet, Khilola P2-104
- Hannema, Sabine P1-10, P1-157, P1-167, P2-257
 Hannema, Sabine E P1-262
 Hanschkow, Martha FC4.2
 Hansen, Dorthe P2-215
 Haqq, Andrea P1-49
 Hara, Kaori RFC12.3
 Hara, Mitsuhiro P1-333
 Harari-Shaham, Amalia P3-281
 Harasymiw, Lauren RFC13.1
 Haris, Basma P1-189
 Harley, Vincent P1-124
 Harraway, James P1-65
 Harrison, Barney RFC11.1
 Hart, Dirk P1-264
 Hart, Roger T4
 Hart, Stephen FC9.1, P1-311
 Hartleif, Stefan P1-12
 Hartmann, Michaela F. FC9.4, P1-158, P1-2, P1-301, P1-53, P1-7
 Hartmann, Micheala P1-4
 Hasbellaoui, Fella P2-280
 Hasegawa, Tomonobu P1-115, P1-275, P2-217, P2-249, P3-27
 Hasegawa, Yukihiro P1-140, P1-173, P1-290, P1-298, P1-416, P2-252, P3-54
 Haseyama, Keiji P2-30
 Hashem, Rania P1-320
 Hashemian, Somayyeh P2-202
 Hashemipour, Mahin P3-105
 Hashim, Raihana P2-80, P3-291, P3-304, P3-322
 Hassan Ahmed Emam, Mohamed P2-11
 Hassan, Heba P3-230
 Hassan, Mona LB-17
 Hassan, Samar P3-290
 Hassan, Ayman P2-193
 Hassaneen, Ehab P3-94
 Hassanzadeh Rad, Afagh P3-111
 Hassanzadeh Rad, Afagh P3-72
 Hassina, Benlarbi P2-161
 Hastings, Lucy P1-426
 Hatipoğlu, Nihal P1-244, P3-134, P3-263
 Hatipoğlu, Nihal P2-169, P3-67
 Hatun, Şükrü P2-240
 Haung, Siqi P2-68
 Hauschild, Michael P1-424
 Hawley, James RFC13.2
 Hayden, James P1-259
 Hazan, Filiz P3-124
 Hazar, Volkan P2-235
 Hazem Gouda, Mohamed P2-50
 Hazhir, Nazanin P2-47
 He, Minfei P1-278, P3-223
 He, Xiaohua P1-61
 He, You RFC6.1
 Hebenstreit, Doris P2-247, RFC10.1
 Hedjadi, Ghazal FC6.1
 Heidari, Abolfazl P1-24
 Heijboer, A.C. RFC9.2
- Heinen, C.A. RFC9.2
 Heinrichs, Claudine P1-86, P2-237
 Heistermann, Johanna T18
 Heldt, Katrin P2-49
 Helleberg, Hans P1-363
 Hellenga, Ilse RFC11.6
 Helvacıoglu, Didem P1-175, P1-176, P1-273, P1-402, P2-52
 Helvacıoglu, Didem P1-116
 Helvacıoglu, Didem P3-202
 Henderson, Mélanie P1-197, P1-337, P1-57
 Henderson, Stuart P1-266
 Henic, Emir P1-419
 Hennig, Matylda P2-100, P3-66
 Henriksen, Louise T4
 Heo, You Jung LB-21
 Herle, Marion P2-187
 Hermanns, Pia FC5.5
 Hermoso, Florinda RFC1.4
 Hermus, Ad RFC2.5
 Hernandez, Ana Maria P3-286
 Hernández-Soto, Rocio P2-118
 Hernández-Soto, Rocío P1-331
 Hero, Matti P1-395, P1-88, T15
 Herrero, Leticia P3-99
 Herrero, Xavier P1-282
 Herrmann, Gloria P1-51
 Hershkovitz, Tova P1-32
 Herzovich, Viviana LB-26
 Hess, Melanie FC7.2, P1-179
 Hetman, Marta LB-19
 Hewitt, Jacqueline P1-124
 Hidesh, Guy RFC3.3
 Hiess, Manuela P1-261, P1-271, P2-247
 Hietämäki, Johanna P1-395
 Higham, Claire P1-10, P1-167
 Higuchi, Shinji P1-173, P1-290
 Hilczer, Maciej P1-355, P2-242
 Hindmarsh, Peter RFC5.4
 Hinojosa, Jose Jiménez LB-20
 Hiort, Olaf P2-205, RFC10.4, RFC3.1, T7
 Hirsch, Harry P3-16, RFC3.3
 Hirschfeldova, Katerina P2-281
 Ho, Chug Shun P1-158
 Ho, Chung Shun P1-7
 Ho, Cindy Wei Li P1-44
 Ho, Clement K.M. P1-67, P2-41
 Ho, Wei-li Cindy P3-1
 Hoad, Kirsten P1-158, P1-7
 Hoang, Thi Diem Thuy P3-213
 Hochberg, Ze'ev P1-53, P1-59
 Hoebcke, Piet P1-261, P1-271
 Hoek, Annemieke LB-12
 Hoeppner, Wolfgang T7
 Hoermann, Henrike P1-211
 Hoey, Hilary RFC14.5
 Hoffmann, Elisa P1-231, P1-380
 Hoffmann, Georg F. FC5.5
 Hofman, Paul FC14.4, FC7.4, P1-50

Hojo, Hironori RFC15.5
 Hokken-Koelega, Anita FC12.3, FC14.6, FC8.3, P1-366, P1-389, P2-126, P3-178
 Hokken-Koelega, Anita C.S. P1-367
 Hokken-Koelega, Anita CS P1-52
 Holder, Martin P1-179
 Holl, Reinhard W. P1-179
 Holl, Reinhard Walter FC7.6
 Hollanders, Jonneke J. FC13.4
 Holm Petersen, Jørgen FC14.2
 Holmgren, Anton P1-119, P1-250, P1-59, RFC12.6
 Holmlund, Mariell P2-220
 Holterhus, Paul Martin P2-20
 Holterhus, Paul-Martin LB-3, P1-12, RFC10.4
 Homaei, Ali P1-24
 Homma, Keiko P3-27
 Homma, Thais K RFC8.4
 Hong, Chen RFC5.6
 Hong, Janet P1-403
 Hong, Sung-Won P3-88
 Hong, Ye P2-121
 Hong, Yong Hee P3-38
 Hong, Young Hee P2-139
 Hong, Yun-Chul P1-40, P1-431, T10
 Honig, Adriaan FC13.4
 Honma, Keiko P2-249
 Hooker, Angelo LB-12
 Hoole, Thabitha P2-80
 Hopper, Neil P1-327
 Hori, Naoaki P1-275, P2-217
 Horikawa, Reiko FC14.5, LB-1, P1-243, P1-406
 Horvath, Tamas L. FC8.1
 Hou, Lele P1-182, P3-89
 Hou, Lele P1-183, P1-232, P2-197
 Hou, Lele P2-68
 Hou, Ling P2-246, P2-54, RFC1.5
 Houang, Muriel P1-303
 Hough, Amy P1-123
 Houghton, Jayne RFC9.4, RFC9.5
 Houzelstein, Denis FC10.3
 Hovnik, Tinka T12
 Hovsepian, Silva P3-105
 Howard, Sasha FC15.4
 Howard, Sasha R. FC8.5
 Hoyer-Kuhn, Heike T18
 Hristozova, Hristina P1-350
 Hu, Lin RFC4.1
 Hu, Xuyun P3-154
 Huang, Dan P2-125
 Huang, Fengyang P1-43
 Huang, Ke RFC4.1
 Huang, Ke P1-200, P2-121, P2-27, P2-29, RFC4.2
 Huang, Lana P1-104
 Huang, Siqi P1-182, P3-89
 Huang, Siqi P1-183, P1-61, P2-197
 Huang, Xiaodong P1-277

Huebner, Angela FC13.1, P2-205
 Hughes, CR RFC13.5
 Huh, Juyoung P1-101
 Huh, Rimm LB-15, P1-268, P2-283, P3-123
 Huljev Frkovic, Sandra P2-179
 Hulshoff-Pol, Hilleke FC13.2
 Huma, Zilla P3-196
 Hunter, Janel P1-25
 Huopio, Hanna RFC15.4
 Hussain, Khalid FC15.2, FC9.1, P1-207, P1-311
 Hussain1, Khalid P1-189
 Hutana, Adina P1-358
 Huynh, Tony P1-65
 Hwa, Vivian P1-365
 Hwang, Il Tae LB-23, P1-174, P1-372, P1-407, P1-75
 Hwang, Jin Soon P1-138, P2-175, P2-184
 Hyradfar, Ataollah P2-47
 Höglér, Wolfgang FC2.1, FC2.1, FC2.2, P1-172, RFC2.1, RFC6.5
 Höybye, Charlotte P1-227
 Højby Rasmussen, Michael P1-371, RFC14.6
 Højgaard, Brigitte P1-114
 Hällqvist, Jenny RFC11.3

I

I, Takashi P1-170
 Iacovidou, Nicoletta P1-118
 Iancu, Mirela P3-39
 Iavatso, Evangelia-Paraskevi P3-236
 Ibañez, Lourdes P1-56, P2-127
 Ibba, Anastasia P2-132, P2-232
 Ibragimov, Zafar P1-325
 Ibragimova, Elvira P1-325
 Ibrahim, Amany P1-141, P1-34, RFC7.3
 Ibrahim, Mohsina P3-228
 Ibrahim, Sandra P2-258
 Ibáñez, Lourdes FC15.5, FC4.3, FC9.3, P1-193, P3-120, RFC4.3, T1
 Ida, Shinobu P1-416, P2-170, P2-252
 Iezzi, Maria Laura P1-401
 Ikiroma, Adalia P1-167
 Ilgaz, Nermin Seda P1-237
 Ilieva, Gordana P3-248
 Im, Minji P2-158
 Im, Sun-Wha FC5.3
 Imel, Erik A. FC2.1, FC2.2, RFC2.1
 Imroda, Nicola P1-120, P1-409, P2-160, P2-287
 In't Hout, Joanna P1-269
 Inoue, Takanobu RFC12.3, T16
 Interator, Hagar P2-6
 Inzaghi, Elena FC7.3, P1-14, P1-386
 Ioakeimidis, Ioannis P3-101
 Ioffe, Irina P2-221
 Iolascon, Achille P1-362

Iotova, Violeta P1-10, P1-167, P1-350, P1-361, P2-149, P2-173, P2-174, RFC10.1, T13
 Irving, Melita P1-215
 Ishankgodjaev, Tokhir P1-325
 Ishiguro, Hiroyuki P1-243
 Ishii, Akira P1-173
 Ishii, Jun FC5.6
 Ishii, Tomohiro P1-115, P1-275, P2-217
 Ismailov, Said Ibragimovich P2-104
 Israeli, Galit P1-265, P2-1
 Itani, Maya P1-381, P2-193, P2-296, P3-153, P3-160, P3-161, P3-28
 Ito, Junko P1-243
 Itonaga, Tomoyo P1-290, P1-298
 Itza, Nerea P2-145, RFC1.4
 Iughetti, Lorenzo P1-106, P1-185, P1-262, P1-401, P1-417, P1-68, P1-97, P2-171, RFC14.3, RFC3.5, RFC7.6, RFC9.6, T19, T6
 Ivannikova, Tatiana P1-69
 Ivanov, Dmitry P2-221
 Ivanova, Antoaneta T13
 Ivarsson, Sten-A. RFC14.5
 Iwanaga, Kogoro P3-69
 Iwata, Fujihiko P1-333
 Izawa, Masako P1-298
 Izumita, Yukie P3-54, P3-63
 Işık, Esra RFC6.4
 Işık, Fatma Büşra P1-145

J

Jacobson, Roi P2-1
 Jacques, Tom RFC11.1
 Jafari, Seyyedeh Forough P3-111
 Jafarzadeh esfahani, Reza P2-202
 Jain, Rakhi P3-319
 Jaja, Tamunopriye P3-294
 Jakimovski, Dejan P3-284
 James, Syril P2-226
 Janchevska, Aleksandra P1-149, P2-216
 Jancova, Emilia P2-91
 Jang, Kyung Mi P3-15
 Jang, Kyung-Mi FC1.2
 Janner, Marco P1-164
 Janu, Dominik P1-76
 Januś, Dominika P3-280, P3-288
 Jaremko, Jacob L P2-34
 Jasinskiene, Edita P2-70
 Jathanakodi, Shrihari P1-387, P1-87
 Jauch, Ralf FC10.3
 Jauhari, Praveen P2-290
 Javanmardi, Alireza FC6.2
 Jayamanne, BDW P1-370
 Jayasena, Arundathi P1-266
 Jazbinšek, Sončka RFC3.6
 Jaźdżewski, Krystian P2-278
 Jean-Louis, Martineau FC5.4
 Jee, Youn Hee FC15.1, RFC15.5
 Jennings, Melissa FC15.1

- Jensen, Rikke Beck RFC14.5
 Jeong, Hwal Rim P1-407, P3-247
 Jerônimo dos Santos, Tiago P1-39
 Jesuran-Perelroizen, Monique P1-408
 Jia, Shiqi FC15.2
 Jian, Yu P1-219
 Jiang, Zhuan-nan P2-238
 Jiang, Zhuannan P2-68
 Jiang, Zhuannan P1-182
 Jin, Binghan LB-24
 Jin, Dong-Kyu P2-158, P2-282
 Jinna Yuan, Jinna P2-121
 Joanna, Smyczynska P1-77
 Joel, Daphna P2-1
 Johnston, Blair FC2.5
 Jolly, Angad P1-273
 Jones, Jeremy H. FC9.5
 Jones, Timothy FC7.2, P1-35
 Jordanova, Olivera P2-216
 Jorge, Alexander A L RFC8.4
 Jorgensen, Anne FC10.3
 Jorro, Facundo P1-240
 Joseph, Shuko FC2.5
 Joshi, Rajesh P2-22
 Jour, Celine P1-381, P2-193, P3-28
 Jouret, Béatrice P1-139
 Jovanovska, Anamarija P3-307
 Joy, Christopher P1-65
 Julier, Cecile P1-322
 Jung, Hae Woon P3-103, RFC7.4
 Jung, Kyeong Cheon FC5.3
 Jung, Min Ho P2-166, P2-85
 Jung, Minho P1-233, P2-122, P2-218, P3-117
 Jung, Mo Kyung P2-165, P2-78
 Jurado, Francisca Rocío Liñán LB-20
 Juriaans, Alicia P1-389
 Juul, Anders FC11.6, FC14.2, P1-136, P1-399, RFC14.5, T4
 Juul, Rasmus Vestergaard FC14.5
 Júlíusson, Pétur P1-267
 Júlíusson, Pétur B. P1-110, P1-258
 Jürimäe, Jaak P1-17
- K**
 Kabolova, Kseniya P3-224
 Kadan, Elcin P1-255
 Kafetzi, Maria P3-102, P3-126
 Kafia, Zichi P1-292
 Kagami, Masayo P1-140, RFC12.3, T16
 Kahaly, George P1-148
 Kahina, Mohamedi P2-161
 Kahveci Çelik, Sinem P1-285
 Kahveci, Hasan P1-71
 Kaleva, Valeriya P1-350
 Kalifa, Rachel RFC10.6
 Kalinchenko, Natalia P1-415
 Kalinchenko, Natalya P2-250
 Kalinin, Alexey P1-405
 Kalinin, Pavel FC11.5
- Kallali, Wafa P2-77, P3-238
 Kallali, Wafa P2-2
 Kallefullah Mohammad, Jasmina RFC9.4
 Kallel, Faten P3-206
 Kallio, Sampo T15
 Kaloumenou, Eirini P1-96
 Kalsbeek, Andries FC13.4
 Kamasaki, Hotaka P1-173
 Kamel, Alaa P2-256, P3-230
 Kamel, Noha P3-309
 Kamenicky, Peter FC2.3, P1-23
 Kamimaki, Tsutomu P2-217
 Kamimura, Miki P2-285, P3-27
 Kamma, Hiroshi FC5.6
 Kammoun, Hassen P3-25
 Kammoun, Thouraya P3-25
 Kamoun, Thouraya P1-322, P1-94, P2-39, P3-170, P3-229, P3-97
 Kamperis, Konstantinos P1-136
 Kamrath, Clemens P1-2, P1-301, P2-66, P3-4
 Kamupira, Sheilah P2-18
 Kanaka-Gantenbein, Christina FC1.3, P1-118, P1-154, P1-242, P2-204, P3-192
 Kandemir, Nurgun P1-404, P2-223, P2-224, P2-59
 Kaneva, Radka P1-153, P1-307
 Kang, Seok Jin P1-216
 Kang, Seok Jin P1-217, P2-24, P2-276
 Kanneman, Ana P1-410
 Kanno, Junko P1-243, P2-285, P3-27
 Kanumakala, Shankar P1-227, P2-178
 Kapczuk, Iga P2-134, P2-286
 Kapellen, Thomas Michael FC7.6
 Kaplan, Emel P1-112
 Kaplan, Emel Aytaç RFC8.1
 Kapoor, Ritika P2-231
 Kapoor, Ritika R P1-215
 Kapusta, Livia P1-388
 Kara, Cengiz P1-162
 Karabouta, Zacharoula P3-184, P3-53
 Karaca, Mehmet Salih P1-254
 Karaca, Serra P1-236
 Karacan Kucukali, Gulin P1-181
 Karacan Kücukali, Gülin P2-119
 Karacay, Seray P1-237
 Karachalioi, Feneli P1-74, P2-214, P2-40, P3-190
 Karakilic Ozturan, Esin P2-270
 Karakilic-Ozturan, Esin P2-45
 Karakılıç Özturan, Esin P1-145, P2-195
 Karalexi, Maria P2-214
 Karalis, Vangelis P1-198
 Karaman, Birsen P1-134, P1-306, P1-390
 Karamfilova, Teodora T13
 Karanes, Sathit P2-26
 Karanikas, Haralampus P2-140
 Karaoglan, Murat LB-28, P1-112, P2-288, RFC8.1
- Karaoglan, Murat P1-353
 Karatza, Eleni P1-198
 Karavidopoulou, Youla P3-101
 Kardaş, Burcu P1-91
 Kardelen Al, Asli Derya P2-270, P2-45
 Kardelen Al, Aslı Derya P1-145, P1-390
 Kardelen, Aslı Derya P1-236, P2-137
 Karelín, Alexander P2-109
 Karem, Mona P3-309, SS1.2
 Kareva, Maria P1-165, P1-206, P1-357, P1-69, P2-201, P2-212, P2-9
 Karges, Beate P1-179
 Karimov, Khamid P1-325
 Kariyawasam, Dulanjalee P2-226
 Karkova, Tatyana P3-129
 Karpf, David FC14.4
 kasap, nurhan P1-116
 Kasatkina, Vladimir P2-109
 Kasatkina, Elvira P2-245, P3-242
 Kasner, Charlotte FC9.4
 Kasongo, Laura P1-70, P2-83, P3-194, P3-257
 Kasparaviciene, Jurate LB-9
 Kassari, Penio P2-140, P3-101, P3-96
 Kassif, Eran RFC5.5
 Katkat, Nancy P1-288
 Katsibardi, Katerina P3-302
 Katsumata, Noriyuki P1-275
 Katsuya Toma, Ricardo P1-199
 Kattamis, Antonis P3-302
 Katugampola, Harshini RFC5.4
 Kauli, Rivka P3-273
 Kawai, Masahiko P3-69
 Kawai, Masanobu P1-243, P1-416, P2-170, P2-252
 Kawamura, Haruka P1-170
 Kawamura, Tomoyuki RFC1.1
 Kawano, Atsuko P2-230
 Kawashima, Sayaka P1-140, RFC12.3
 Kawashima-Sonoyama, Yuki T16
 Kay, Raissa FC10.3
 Kaya, Abdulkadir P1-71
 Kaygusuz, Sare Betul P1-175, P1-176, P1-273, P1-402, P2-25, P2-52, P3-202, P3-80
 Kaygusuz, Sare Betul P1-3
 Kayhan, Gülsüm P1-103
 Kazachenko, Natalia P2-221
 Keelan, Jeffrey T4
 Keevil, Brian RFC13.2
 Keinan-Boker, Lital LB-5
 Kelishadi, Roya P3-105
 Kelmanson, Igor P1-256
 Kemp, Elizabeth P2-36
 Kempf, Elena P2-110
 Kendall, Deborah P1-38
 Kendirci, Mustafa FC11.2, P1-244, P3-134, P3-263
 Kendirci, Mustafa P2-169, P3-67
 Kenis, Vladimir P2-35

- Kerkhof, Gerthe P1-366
 Kerkouche, Soraya P3-128
 Kerry, Eleanor P1-375
 Keselman, Ana P1-72
 Keskin, Mehmet P1-112, P1-162, P2-288, RFC8.1
 Keskin, Mehmet P1-353
 Keskin, Meliksah P1-181
 Keskin, Melikşah P1-330
 Keskin, Melikşah P2-101
 Keum, Changwon P3-15
 Khadilkar, Anuradha P2-38, P3-82
 Khadilkar, Vaman P2-38, P3-82
 Khalifa, Anissa P2-280
 Khalil, Ahmed P2-156, P2-296, P3-153, P3-160, P3-161
 Khalsi, Fatma P2-77
 Khan, Faiyaz P1-189
 Kharkova, Mariia P3-121
 Khater, Doaa P1-11, P3-73
 Khawaja, Nahla RFC15.6
 Khayat, Morad P1-430
 Khemiri, Monia P2-77
 Khiari, Mohamed El-Mokhtar P3-113
 Khlaifia, Zied P2-77
 Khlairit, Patcharin P1-201
 Khlifi, Asmaa P3-240
 Kiess, Wieland CON1.2, FC4.2, P1-30, P2-110, RFC4.4
 Kieviet, Noera RFC13.3
 Kiaev, Aleksei P2-219
 Kikuchi, Nobuyuki RFC1.1
 Kikuchi, Toru RFC1.1
 Kilic, Semih P1-3
 Kim, Seulki P3-117
 Kim, Shinhee P3-117
 Kim, Yangho P1-40
 Kim, Bung-Nyun P1-431, T10
 Kim, Chan Jong P1-368
 Kim, Dong Ho P3-156
 Kim, Eun Young P1-174, P1-372, P1-75, P2-241, P3-172
 Kim, Ga Hyun P2-276
 Kim, Goo Lyeon P1-184, P3-64
 Kim, Gu-Hwan P1-101, P2-209, P3-179
 Kim, Hae Soon P1-40
 Kim, Heung Sik P1-216, P1-217, P2-24, P2-276
 Kim, Ho-seong FC8.6
 Kim, Hwa Young P1-431
 Kim, Hye Young P1-429
 Kim, Hyun-Ji P1-385, P1-62, P3-13
 Kim, Jae Hyun LB-23, P1-340, P1-349, RFC7.4, T10
 Kim, Jaehyun P1-339
 Kim, Ji Hyun P3-156
 Kim, Johanna Inhyang P1-431, T10
 Kim, Jong-Il FC5.3
 Kim, Kyoung-Nam P1-431
 Kim, Min-Sun P2-158, P2-282
 Kim, Se Jin P1-216, P1-217, P2-24, P2-276
 Kim, Se Young P1-340
 Kim, Seon Young P1-83
 Kim, Seulki P1-233, P2-122, P2-218, P2-85
 Kim, Shin Hye P2-158
 Kim, Shin-Hee P2-85
 Kim, Shin-Hye P1-203
 Kim, Shinhee P1-233, P2-218
 Kim, Yoo-Mi P1-83, P2-209
 Kim, Young Mi P1-429
 Kimura, Toru FC5.6
 Kinare, Arun P3-82
 Kinjo, Kenichi P1-406
 Kino, Tomoshige FC13.6
 Kirel, Birgul P1-162
 Kirk, Jeremy RFC14.5
 Kirkgoz, Tarik P1-3, P1-402, P3-80
 Kirkgoz, Tarik P1-116, P1-175, P1-176, P1-273, P2-52
 Kirköz, Tarik P3-202
 Kirstein, Anna RFC4.4
 Kiseleva, Elena P2-245, P2-261, P3-242
 Kiselyova, Elena P1-147
 Kisileva, Elena P3-253
 Kitamura, Miyuki P2-230
 Kitaoka, Taichi P1-168
 Kiykim, Ayca P1-116
 Kjellberg, Emma P1-195
 Klaskova, Eva LB-27
 Klatka, Maria T5
 Klaushofer, Klaus FC6.1, RFC15.5
 Kleanthous, Kleanthis P1-16, P3-301
 Klee, Dirk P1-204
 Klee, Philippe P2-264, P3-84
 Kleinendorst, Lotte P1-196, P1-46, P1-47
 Klepochova, Radka FC2.4
 Kliesch, Sabine LB-3
 Klink, Daniel RFC11.6
 Klitsenko, Olga P3-55
 Klopstock, Tehila P1-128, RFC3.3
 Klose, Daniela P2-269
 Klutmann, Carina FC5.5
 Klöting, Nora P1-42
 Klünder-Klünder, Miguel P1-15
 Kmiha, Sana P1-322, P1-94, P3-170
 Ko, Cheol Woo P3-305
 Ko, Cheol-Woo FC1.2, T14
 Kobyakova, Olga P1-328
 Koceva, Svetlana P3-284
 Koch, Gilbert FC7.2
 Kochar, Inderpal P2-94
 Kochar, Indrapal singh P3-319
 Kochar, IPS P2-206
 Kocheva, Svetlana P3-307
 Kocova, Mirjana P2-263
 Koehler, Birgit RFC10.1
 Koehler, Katrin FC13.1
 Kofteridis, Diamandis P3-192
 Koga, Yasutoshi P2-230
 Kohlsdorf, Katja RFC11.5, RFC7.2
 Kokai, George P2-180
 Koks, Carolien LB-12
 Kolanowska, Monika P2-278
 Kolasa-Kicińska, Marzena P1-355, P2-242
 Koledova, Ekaterina FC12.5, P1-220, P1-221, P2-159, P2-194
 Koleva, Reni P3-95
 Kollurage, D Udeni Anuruddhika P1-370
 Kollurage, Udeni P2-80
 Kolodkina, Anna P1-55, P2-250, P2-35
 Kolomina, Irina P3-253
 Kolouskova, Stanislava FC12.2, RFC14.2, RFC6.6
 Koloušková, Stanislava P2-69
 Komatsu, Nagisa P3-54
 Kong, Yuanmei P1-297
 Koniari, Eleni P3-275
 Konovalov, Alexandre FC11.5
 Konrad, Daniel P2-271, RFC10.1, RFC10.5
 Konrad, Martin P2-53
 Konstantynowicz, Jerzy P2-36
 Kontaki, Helen P2-214
 Koohmanae, Shahin P3-72
 Koohmanae, Shahin P3-111
 Kopacek, Cristiane P1-155
 Koprulu, Ozge P3-124, P3-2
 Körner, Antje
 Kor, Yilmaz S1.1
 P1-207, P2-99, P3-259
 Kor, Yilmaz P3-22
 Korbonits, Marta P1-10, P1-157, P1-167, RFC10.1, RFC11.1
 Korkin, Anatoly P2-35
 Korkmaz, Huseyin Anil P3-36
 Korman, Luciano P1-240
 Korpal-Szczyrska, Maria FC14.4, P2-163
 Korpela, Katri T15
 Kortmann, Barbara P1-269
 Kortmann, Rolf-Dieter P1-398
 Korula, Sophy P1-169, P2-79
 Kosaki, Rika P1-140
 Koshmeleva, Marina P1-328
 Kosovtsova, Hanna P3-211
 Kostalova, Ludmila P2-168
 Kosti, Evangelia P3-96
 Kostopoulou, Eirini P3-48, P3-68
 Kosvyra, Alexandra FC7.1
 Kotan, Damla P3-198
 Kotan, Leman Damla RFC15.2, RFC8.5
 Kotanidou, Eleni P FC7.1, P2-301
 Kotnik, Primož RFC3.6, T12
 Kotori, Afrim P3-42
 Kouhnavař, Marjan P1-146
 Kourlaba, Georgia P3-96
 Koutroumpa, Arsinoi P1-198
 Koutsiana, Elisavet FC7.1

- Kovalenko, Tatiana FC14.4, P2-124
 Kovalenko, Tatyana P1-78, P2-185
 Kovatchev, Boris PL8
 Kovač, Jernej P1-109, T12
 Koyama, Satomi P2-189
 Kozioł-Kozakowska, Agnieszka P3-280, P3-288
 Koç, Altuğ P3-159, P3-19
 Krajewska, Maria P3-130
 Krall, Christoph RFC10.1
 Kraria, Loubna P1-126
 Kratochvílová, Simona FC6.3
 Krause, Marianna T4
 Krawczyk, Sylwia P2-286
 Krebs, Andreas P2-32
 Krepel Volsky, Sari T17
 Kristensen, Kurt P1-136
 Kristiansen, Eva P1-22
 Kristina, Kokoreva P3-224
 Kriström, Berit P1-227, P2-220, P2-229
 Krnic, Nevena P1-36, P2-10, P2-179
 Krone, Nils P1-167, RFC10.1
 Krone, Nils P FC10.1, FC15.3, P1-10, P1-6, RFC13.2
 Krone, Ruth P1-10, P1-157, P1-167, P1-370, P1-6, RFC10.1, RFC13.2
 Krssak, Martin FC2.4
 Krstevska-Konstantinova, Marina P1-149, P3-248, P3-284
 Krude, Heiko P1-156
 Krull, Simone P2-66, P3-4
 Kubiak, Anna P2-278
 Kubo, Yoshihiro FC5.6
 Kubota, Takuo P1-168
 Kucerova, Petra FC12.2, P1-317, RFC14.2, RFC6.6
 Kucharska, Anna P2-93, P3-130, P3-132
 Kucharska, Anna M. P1-73
 Kucukemre Aydin, Banu P1-283
 Kuczynski, Adam RFC11.1
 Kuitonen, Mikael T15
 Kukkonen, Anna Kaarina T15
 Kulich, Michal P2-69
 Kulikova, Kristina P2-35
 Kulle, Alexandra LB-3, P1-42
 Kum, Chang Dae P1-138, P2-175, P2-184
 Kumar, Ashok P1-276
 Kumar, Manoj P1-276
 Kumar, Pardeep P1-130
 Kumar, Shruti P2-18
 Kummer, Sebastian P1-204, P1-211, P2-20
 kumru, burcu P1-353
 Kuppens, Renske FC12.3
 Kure, Shigeo P2-285, P3-27
 Kurnaz, Erdal P1-160, P1-241, P1-71, P2-119, P3-225
 Kurolap, Alina P1-32
 Kurtoglu, Selim FC11.2
 Kurtoğlu, Selim P1-244, P3-134, P3-263
- Kurtoğlu, Selim P2-169, P3-67
 Kusec, Vesna P2-10
 Kutbay, Yaşar B. P2-12
 Kutbay, Yaşar Bekir P3-159
 Kutin, Maxim FC11.5
 Kutlu, Esra P1-396
 Kuulasmaa, Teemu RFC15.4
 Kuzevska-Maneva, Konstandina P3-284
 Kuzmanovska, Maja P2-263
 Kuzmenkova, Elena P3-191
 Kuznetsov, Nikolay RFC5.3
 Kučerová, Petra P2-63
 Kvacheniyk, Dmytro P3-262
 Kvernebo-Sunnergren, Kjersti RFC11.4
 Kwak, Min Jung P1-429
 Kwak, Soo Heon P1-184, P3-64
 Kwon, Ahreum FC8.6
 Kwon, Eun Byul P3-247
 Kyheng, Christèle P1-23
 Kyriako, Andreas P1-6
 Kyriakou, Andreas P1-125, RFC13.2, RFC2.6, RFC8.3
 Kyrylova, Olena P2-86
 Kyskova, Slavomira P2-168
 Kämpe, Anders RFC6.3
 Kärkinen, Juho P1-88
 Köprülü, Özge P1-27, P2-12, P3-19, P3-233
 Körber, Ingrid P1-51, RFC11.5
 Körner, Antje FC4.2, P2-110
 Kühnen, Peter FC15.2
 Küme, Tuncay P1-335
 Küpçü, Zekiye P1-103, P2-44, P3-56
 Kilinç Uğurlu, Aylin P1-103, P1-351, P2-103, P2-44
 Kilinç, Suna FC7.5, P1-208, P1-294, P1-60
 Kir, Metin FC6.4
 Kirankaya, Ayşegül P1-294, P1-60
 Kirbyık, Ozgur P3-2
 Kirbyık, Özgür P1-321, P3-215
 Kirkgoz, Tarık P1-53
- L**
 L'Allemand, Dagmar P2-49
 La Barbera, Andrea P1-194, P1-336, P2-181
 La Grasta Sabolić, Lavinia P3-231
 La Manna, Angela P1-45
 La Rocca, Cinzia P1-260, P1-58
 Laakso, Markku RFC15.4
 Laakso, Saila FC3.6
 Labochka, Dominika P2-93, P3-130
 Lacamara, Nerea P3-276
 Laccone, Franco RFC15.5
 Laczmanska, Izabela LB-19
 Ladha, Tasneem P3-167
 Ladjouze, Asmahane P1-296, P3-128
 Laham, Muhamnad P2-193
 Laimon, Wafaa P2-82, P3-71
- Lall, Paula P1-124
 Lambalk, Cornelis LB-12
 Lambert, Anne-Sophie FC2.3, P1-23, RFC2.2
 Lambert, Anne-sophie P1-213
 Lambregtse-van den Berg, Mijke RFC13.3
 Lami, Francesca P1-185
 Landau, Zohar RFC7.5
 Landgraf, Kathrin FC4.2
 Landini, Samuela P1-336, P2-181
 Lane, Laura MTE 7
 Lang-Muritano, Mariarosaria P2-271, RFC10.5
 Langham, Shirley RFC5.4
 Lanzenberger, Rupert S6.1
 Laptev, Dmitry P1-332
 Larionova, Maria P2-124
 Larizza, Daniela P1-323, P1-428, P2-64, P3-115, P3-98
 Larom, Gal P3-281
 Laron, Zvi P3-273
 Larrivée-Vanier, Stéphanie FC5.4
 Lassoued, Najoua P3-91
 Latorre Martinez, Esther P3-293
 Latrech, Hanane P3-142, P3-147, P3-148, P3-86
 Latrech, Hanane P2-274, P3-240
 Latronico, Ana C P1-262
 Latronico, Ana Claudia RFC8.2
 Latyshev, Dmitry P3-129
 Latyshev, Oleg P1-147, P2-245, P2-261, P3-129, P3-242, P3-253
 Lauffer, Peter P1-223
 Lauriola, Silvana P1-5, RFC9.3
 Lausch, Ekkehart P2-32
 Lavi, Eran P1-128, RFC10.6
 lavi, Eran FC11.3
 Lavrova, Tatyana P1-147
 Law, James P1-352, P1-384, P3-155
 Lazar, Liora P1-187, P1-291, T17
 Lazreg, Youssef P2-274
 Lazzati, Juan Manuel P1-249
 Lazzeroni, Pietro FC3.2, RFC14.3
 Lațcu, Manuela Ioana P2-116
 Le Bouc, Yves FC12.1, LB-11
 Le Ru, Romain FC10.3
 Le Stunff, Catherine RFC15.1
 Leary, Sam D. FC1.5
 Lebane, Djamil P3-176, P3-201
 Lebenthal, Yael P1-347, P2-1, P2-6, T17
 Lebl, Jan FC12.2, LB-27, P1-317, P2-281, P2-63, RFC14.2, RFC6.6
 Lebrethon, Marie-Christine P3-254
 Lee, Beom Hee P2-209
 Lee, Ga Hyun P1-216, P1-217, P2-24
 Lee, Hae Sang P1-138, P2-175, P2-184
 Lee, Heirim P1-429
 Lee, Jae Hee P2-241
 Lee, Ji-Min FC1.2, T14
 Lee, Jieun P1-349

- Lee, Joon Seok P3-305
 Lee, Kee-Hyoung LB-15, P1-268, P2-283, P3-123
 Lee, Kevin P1-65
 Lee, Miseon P3-305
 Lee, Na Yeong P3-174
 Lee, Nayeong P3-117
 Lee, Nayoung P1-233
 Lee, Sae-Mi P1-429
 Lee, Samantha Lai-Ka FC3.5
 Lee, Seong Yong RFC7.4
 Lee, Seonhwa P1-233, P2-218, P2-85, P3-117
 Lee, Su-Jung FC1.2, T14
 Lee, Yena P1-101, P2-209, P3-179
 Lee, Yoonji P1-233, P3-117
 Lee, yoonji P2-122
 Lee, Young Ah FC5.3, LB-21, LB-23, P1-431, RFC7.4, T10
 Lee, Yun Jeong LB-21
 Lee, Yung Seng P1-44
 Lee, Yung-seng P3-1
 Leff, Jonathan FC14.4, P1-235, P1-84
 Legendre, Marie P1-257, P1-80
 Leger, Juliane RFC3.2
 Leger, Julienne FC10.3
 Lehrian, Theresia P1-380
 Lehrian, Thersia P1-231
 Leis, Rosaura P1-33, P1-345, P3-119
 Leite, Ana Luisa P1-253
 Leite, Ana Luísa LB-16, P3-315
 Leiva-Gea, Isabel LB-20
 Leka-Emiri, Sofia P1-432, P2-251
 Lekka, Eirini P3-101
 Lemos, Manuel C. P3-318
 Lemos-Marini, Sofia Helena Valente P1-85
 Leniz, Asier P3-320
 Lennerz, Belinda RFC11.5
 Leo, Francesco T6
 Leonardi, Salvatore P2-75
 Leonovich, Anastasiia P3-177
 Leopoldino, Andréia RFC13.4
 Lepage, Benoit P1-139
 Lerin, Carles FC15.5
 Leroy, Patricia P3-254
 Leschek, Ellen W. FC15.1
 Lesosky, Maia P1-1
 Leunbach, Tina Lund P2-215
 Levek, Noah RFC7.5
 Levi, Tgst RFC10.6
 Levine, Michael A. P2-146
 Levy Shraga, Yael LB-25
 Levy-Khademi, Floris P1-128, P3-16, P3-296
 Levy-Lahad, Ephrat FC11.3
 Levy-Lahad, Ephrat P1-128, P3-296, RFC3.3
 Levy-Shraga, Yael RFC7.5
 Lewiński, Andrzej P1-355, P2-242
 Lewsey, James P1-167
 Li Pomi, Alessandra P2-147, P2-186
 Li, Dan P1-61
 Li, Guoqiang P1-277, P2-188
 Li, Juan P1-277, P2-188, T20
 Li, Liang RFC5.6
 Li, Nan FC15.3
 Li, Niu P1-225, P1-277, T20
 Li, Pin P1-304, P1-326
 Li, Pinggan P1-182
 Li, Qiang RFC6.1
 Li, Rui RFC6.3
 Li, Wenjing P1-316
 Li, Wenjing P2-222, P3-14
 Li, Xiaojing P2-95, P3-197, P3-24
 Li, Xin P1-225, P2-188, P2-188, T20
 Li, Yan P1-326
 Li, Yanhong P2-114, P3-193, P3-222
 Li, Yanhong P3-151, P3-6
 Li, Yanhong P3-241, P3-44
 Li, Yuchuan P3-154
 Liang, Li FC1.1, P1-278, P1-297, P2-121, P3-223
 Liang, Li-yang P2-238
 Liang, Liyang P2-68
 Liang, Liyang P1-182, P3-89
 Liang, Liyang P1-183, P1-232, P2-197
 Liang, Suisha P1-49
 Liang, Xinyi P2-29, RFC4.2
 Liang, Xuejun P1-316, P3-60
 Liang, Yan P2-246, RFC1.5
 Lichiardopol, Corina P1-10
 Lightman, Stafford PL3
 Lignitz, Sarah P3-258
 Lilos, Pnina P3-273
 Lim, Han Hyuk P1-83
 Lim, Jung Sub P1-138, P2-175, P2-184, P3-156
 Lim, Kyung In P1-138
 Lim, Sharon P3-212, P3-214
 Lim, Youn Hee LB-21
 Lim, Youn-Hee P1-431, T10
 Lim, Yvonne Yijuan P1-44, P3-1
 Limbert, Catarina P1-253, P2-130, P3-239
 Limond, Jennifer RFC11.1
 Lin, Hu LB-24, P2-121, RFC4.2
 Lin, Jen-Chieh P1-162
 Lin, Juan P3-6
 Lin, Shaofen P1-232
 Lin, Yuezhen P2-37
 Lindsay, Robert P2-2
 Linglart, Agnès FC2.2, FC2.3, FC6.6, P1-18, P1-213, P1-23, RFC2.2, RFC3.1
 Lisboa Gomes, Nathalia P1-135
 Lisitsa, Tatiana P2-109
 Litou, Eleni P2-301
 Liu, Ge-li P3-145
 Liu, Donghai P2-191
 Liu, GeLi P2-121
 Liu, Min P1-316
 Liu, Shijian P1-225
 Liu, Shufang P3-272
 Liu, Xiaojing P3-12
 Liu, Ying P3-218
 liu, ziqin P3-324, P3-325
 Liu, Zulin P1-183, P1-232, P2-197
 Liu, Zulin P2-68
 Liu, Zulin P1-182, P3-89
 Lizarraga-Mollinedo, Esther FC9.3, P2-127
 Lizarralde, Eneritz P2-279
 Lizárraga-Mollinedo, Esther P1-193, RFC4.3
 Llamas-Porras, Salvador P1-331
 Llorca, Maria Laura P1-282
 Llorente Cereza, Maria Teresa P1-229
 Lo Presti, Donatella P2-75
 Lo, Fu-Sung P1-137, P1-383
 Lobanov, Yuri P3-129
 Lobo, Ana Luísa P3-157
 Loch Batista, Rafael P1-135
 Loche, Sandro P2-132, P2-178
 Loh, Siew Kee P1-67
 Loh, Tze Ping P1-158, P1-7
 Lohiya, Nikhil P2-38, P3-82
 Loidi, Lourdes P2-61
 Loke, Kah Yin P1-44, P2-16
 Loke, Kah-yin P3-1
 London, Shira P2-244
 Lonero, Antonella P2-171, P3-287
 Longhi, Silvia P3-267
 Longo, Chiara P1-251
 Lopes, Andreia P3-157
 Lopez Marti, Jessica LB-26
 Lopez, Yeriley P2-176
 Lopez-Gonzalez, Desiree P3-286
 Lorek, Miłosz P1-373
 Lorello, Paola P2-287
 Lorente-Blazquez, Isabel P3-320
 Lorente-Blazquez, Maria Isabel P3-316, P3-333
 Lorraud, Christine P1-80
 Losekoot, Monique P1-228
 Loukil, Fatma P1-94
 Loukopoulou, Sofia P3-96
 Loureiro, Carolina P1-338
 Lovato, Luigi P1-378
 Lovell-Badge, Robin FC11.2
 Lovrečić, Luca T12
 Lu, Wei P3-32
 Lu, Wei P3-197
 Lu, Wen-Li P1-324
 Lu, Wenli P2-81, P3-204, P3-261, T11
 Lubieniecki, Fabiana P1-249
 Luboch-Furmańczyk, Monika P2-100
 Lubov, Samsonova P3-224
 Lucaccioni, Laura P1-262, P1-417, P1-68, RFC9.6
 Lucas-Herald, Angela K RFC10.3

- Lucchi, Simona P1-423
 Lucchini, Giuseppe P3-277
 Lucherini, Barbara P1-194, P1-336, P2-181
 Luczay, Andrea P1-167
 Ludar, Hana P2-244
 Lui, Julian C RFC15.5
 Lui, Julian C. FC15.1
 Lumsden, Daniel P3-327
 Lund, Allan M P3-29
 Lundberg, Elena P2-220, P2-229, P3-7
 Luo, FeiHong P2-121
 Luo, Feihong RFC4.5
 Luo, Feihong P1-186, P2-95, P3-197, P3-24, P3-32, RFC6.1
 Luo, Xiaoping P2-246, P2-54, P3-158, RFC1.5
 Luong, Tin P3-313
 Luongo, Caterina P1-111
 Luongo, Caterina P1-93
 Lupi, Fiorenzo P3-267
 Łupińska, Anna P1-355, P2-242
 Lupski, James R P1-273
 Luque-Romero, Luis P1-331
 Luque-Romero, Luis Gabriel P2-118
 Luther, Sarah P2-108, P3-104
 Lymeropoulos, Giorgos P3-101
 Lyons, Greta P1-286, P1-426
 Lysy, Philippe T9
 López Bermejo, Abel P2-127
 López Martínez, Briceida RFC1.3
 López-Bermejo, Abel FC4.3, FC9.3, P1-193, P1-56, RFC4.3, T1
 López-González, Desireé P1-15
 López-Siguero, Juan Pedro LB-20
- M**
- M Selveindran, Nalini P2-292
 M, El Tantawi P3-70
 M, El-Tekeya P3-70
 M. Cassim, Sumaiya P1-266
 Ma, Xiaoyu P2-81
 Ma, Huamei P3-151, P3-6
 Ma, Huamei P2-114, P3-193, P3-222
 Ma, Huamei P3-241, P3-44
 Ma, Lizhuang T20
 Ma, Xiaoyu P3-204
 Maahs, David S4.1
 Macaluso, Anna P1-360
 Macarulla-Arenaza, Maria Teresa P3-320
 MacGregor, Duncan P1-124
 Maciej, Hilczer P1-77
 Mackay, Deborah NA2
 Mackay, Lindsay P1-158
 Mackay, Lindsey P1-7
 Macqueen, Zoe P1-125
 Madani, Hanan P1-34
 Madeo, Simona F. P1-185, RFC7.6
 Madeo, Simona Filomena T6
 Madi, Jose Mauro P1-155
- Madsen, André P1-110, P1-258, P1-267
 Madsen, Karen P1-49
 Madsen, Mette P2-215
 Maeshima, Ruhina FC9.1
 Maeyama, Takatoshi P2-170
 Maffei, Francesca P1-79
 Maggio, Maria Cristina P1-392, P1-95, P2-192
 Maghnies, Mohamad P1-251, P1-252, P1-391, P1-89, P1-97, RFC11.2, RFC12.5, RFC2.4, T3
 Maglaveras, Nicos P3-101
 Magnani, Cristiana P2-150, P3-133
 Magne, Fabien FC5.4
 Magnusson, Per P1-22
 Mahabier, Eva FC14.6
 Mahachoklertwattana, Pat P1-201, P2-131, P2-26
 Mahameed, Jamal P1-32
 Maharaj, AV RFC13.5
 Maharaj, Avinaash FC13.5
 Maharaj, Avinaash V RFC14.4
 Mahdi, Sundus P1-6, RFC13.2
 Maherzi, Ahmed P2-77
 Mahesh, Buddhika P3-271
 Mahfouz, Amel P3-78
 Mahfouz, Shaymaa P2-265, P3-18
 Mahfouz, shaymaa P2-273
 Mahjoub, Bahri P2-60, P3-91
 Mahmoud Asaad Matter, Randa RFC1.6
 Mahmoud, Ahmed P1-271
 Main, Katharina FC14.2, T4
 Maiorino, Maria Ida T3
 Majcher, Anna P1-73
 Majdoub, Hussein P3-200
 Makaya, Taffy P3-299
 Makazan, Nadezhda P2-212
 Makitie, Outi RFC6.3
 Makitie, Riikka RFC6.3
 Makretskaya, Nina P1-332, P2-157, P2-250
 Makris, Anestis RFC8.3
 Makuch, Magdalena P2-286
 Malaquias, Aleksandra C. RFC8.4
 Malecka-Tendera, Ewa P1-131, P1-41
 Malekpour Dehkordi, Zahra FC4.1
 Maliachova, Olga P1-166
 Malievsky, Oleg P1-361
 Mallet, Delphine P1-296
 Mallucci, Conor P1-102, P1-259, RFC11.1
 Malmusi, Giovanni P1-68
 Malpique, Rita P3-120
 Maltoni, Giulio P2-92
 Malumbres-Chacón, María P3-116
 Malyshева, Natalia P1-165
 Mamadova, Jamala P1-162
 Mamperi, Hedi RFC15.6
 Mancano, Giorgia P2-181
 Mancini, Alessandra FC15.4, FC8.5
- Mandić, Dario P3-231
 Mandy, William P1-375
 Maneva, Elita P3-284
 Maniatis, Aristedes FC14.4
 Manios, Ioannis P2-140
 Manolakos, Emmanouil P3-301
 Manousaki, Despoina RFC6.3
 Mantis, Stelios P3-52
 Mantovani, Giovanna P2-48
 Mantovani, Giovanna FC6.6
 Mantzou, Aimilia P3-275
 Manyas, Hayrullah P1-143, P1-245, P1-308, P1-321, P3-106, P3-159, P3-182, P3-215, P3-226
 Manzoor, Jaida P3-310
 Mao, Meng FC2.1, FC2.2, RFC2.1
 Mao, Shujiong P1-90
 Maouche, Hachemi P3-113
 Maramis, Christos P3-101
 Maranghi, Francesca P1-260, P1-58
 Maratova, Klara FC6.3
 Marchant, Alice P2-210
 Marcondes Lerario, Antonio P1-135
 Marcovecchio, Loredana S4.3
 Marcus, Claude P2-162
 Marette, André P1-197, P1-57
 Marginean, Oana P1-358
 Maria Frade Costa, Elaine P1-135
 Maria, Maleeha RFC15.4
 Marini, Joan C FC6.1
 Marino, Roxana P1-129, P2-259
 Markantonis, Sophia P1-198
 Markidou, Sophia P2-301
 Markosyan, Renata P3-289
 Markovska, Velina T13
 Marmiroli, Nelson FC3.2
 Marolda, Viviana FC5.2
 Marques, Olinda P3-318
 Marta Torrecilla-Parra, Marta FC8.2
 Martelossi, Stefano P3-295
 Marti, Amelia P1-192
 Martin Garcia, Maria P2-128
 Martin, Ayelen FC14.1, P1-359
 Martin, David D FC2.6
 Martin, Silvia P1-364
 Martinerie, Laetitia RFC3.2
 Martinerie, Laetitia FC10.3
 Martinez-Aguayo, Alejandro P2-46
 Martinez-Badás, Itziar P3-276
 Martinez-Brocá, Asuncion P1-331
 Martinez-Calcerrada, Jose-Maria P1-56
 Martins, Sandrina LB-16, P3-315
 Martins, Sofia P3-318
 Martos-Moreno, Gabriel Á. P1-100, P2-21
 Martos-Moreno, Gabriel Ángel P1-376, P2-129
 Martínez, Alejandro P1-338
 Martín-Rivada, Álvaro P1-376
 Martínez-Aguayo, Alejandro P1-274

- Martínez-Calcerrada, Jose-María FC9.3
 Martínez-Villanueva, Julián P2-129
 Marzouk, Eman P2-273
 Marzuillo, Pierluigi RFC11.2
 Marzuillo, Pierluigi FC4.4, P1-354, P1-45
 Mas-Pares, Berta FC9.3, P2-127
 Mas-Parés, Berta P1-193, RFC4.3
 Masindova, Ivica P2-91
 Maslowska, Kamila P2-286
 Masmoudi, Saber P2-266
 Masnata, Maria Eugenia P1-152
 Mason, Avril P1-125, RFC2.6, T19
 Massa, Guy P2-136
 Massey, Jill P3-270
 Massoud, Mohamed Naguib FC4.5
 Mastorakos, George P1-16
 Mastromauro, Concetta LB-13
 Mastubara, Keiko RFC12.3
 Masueva, Madina P1-393
 Masunaga, Yohei T16
 Masunaga, Youhei FC3.1
 Matarazzo, Patrizia P1-106, P1-20,
 P1-400, P1-401, P2-208, P2-232, P3-30
 Materassi, Paola Manera Ada P1-360
 Mathai, Sarah P1-169, P2-79
 Mathiesen, Barbara T4
 Mathiesen, Jes S P2-215
 Mathieu, Marie-Eve P1-197
 Mathieu, Marie-Ève P1-337, P1-57
 Matias, Joana P2-130
 Matsubara, Keiko P1-140
 Matsubara, Yoichi LB-1
 Matsumoto, Fumi P1-416, P2-252
 Matsumoto, Takako P2-230
 Matsumura, Tomohiro RFC6.5
 Matsuo, Nobutake P2-217
 Matteoli, Maria Cristina FC7.3, P2-225
 Matthews, John FC5.1
 Mattoussi, Nadia P3-238
 Mattsson, Mattias P3-7
 Matusik, Paweł P1-41
 Mauro, Vera RFC2.4
 Mavrea, Kalliopi P3-302
 Maximova, Natalia P3-168
 Mayatepek, Ertan P1-204, P1-211,
 P2-144, P2-20
 Mayoral-Sánchez, Eduardo P1-331
 Mazen, Inas FC10.3, P2-256, P3-230
 Mazerkina, Nadezhda FC11.4
 Mazerkina, Nadia FC11.5, P2-219
 Mazor-Aronovitch, Kineret RFC7.5
 Mazzanti, Laura P1-378, P2-182, P3-164
 Mazzarino, Johan P1-408
 Mazzatorta, Diego P1-401
 Małek, Agnieszka P3-288
 Mbanefo, Ngozi P2-199
 McAssey, Karen P1-178
 McBride, Craig P1-65, P2-151
 McCarthy, Margaret S10.1
 McDermott, Helen P2-18
 McElreavey, Ken FC10.3, FC10.4, P1-127,
 P2-244
 McGowan, Ruth RFC10.3
 McMillan, Martin P1-266, RFC10.3
 McNeilly, Jane T19
 McNeilly, Jane D RFC10.3
 Medeiros, Mara P3-286
 Medina Bravo, Patricia
 Guadalupe RFC1.3
 Megged, Orly P3-16
 Megnazi, Ophir LB-25
 Mehany, Sarah N. FC2.4
 Mehdi, Muhammad Zain P2-2
 Mehdiyeva, Humay P1-414
 Meimaris, Eirini FC13.5
 Meinel, Jakob RFC10.4
 Meireles, Carla P3-157
 Meissner, Thomas P1-204, P1-211,
 P2-144, P2-20
 Mejia de Beldjenna, Liliana P3-186,
 P3-199
 Mejorado-Molano, Francisco Javier P2-23
 Mekkawi, Mona P2-256
 Mekkawy, Mona P3-230
 Melhorn, Susan FC4.6
 Melikyan, Maria P1-206, P1-69, RFC9.5
 Mellgren, Gunnar P1-267
 Melliti, Safa P2-77
 Menardi, Rachele P1-401, P2-232
 Mendelova, Eva P2-168
 Mendes, Ana Raquel P3-157
 Mendes, Arthur P2-196
 Mendes, Arthur Francisco P2-57
 Mendonça, Berenice P1-10, P1-167
 Mendonça, Berenice B RFC8.2
 Mendonça, Berenice Bilharinho P3-219
 Mendonça, Berenice B P1-262
 Mendonça, Berenice Bilharino P1-270
 Mendoza, Beatriz P2-297
 Mendoza, Carolina P1-274
 Meng, Lingrui P1-337
 Meng, Zhe P1-182
 Meng, Zhe P2-68
 Meng, Zhe P1-183, P1-232, P2-197,
 P2-238
 Mengel, Eva P1-17
 Mengen, Eda RFC8.5
 Menke, Leonie RFC2.5
 Menon, Smrithi P3-299
 Merad, Mohamed Samir P3-308, P3-329,
 P3-331, P3-332
 Merel, Tiphanie FC10.3, P1-127
 Mericq, Veronica P1-228, P1-399
 Mesa, María D. P1-33
 Messa, Federica RFC11.2
 Messina, Giuseppe P1-392, P1-95
 Messina, Maria Francesca P2-182,
 P2-186, P3-164
 Metherell, LA RFC13.5
 Metherell, Louise A RFC14.4
 Metherell, Lou P2-2
 Metherell, Louise FC13.5
 Metzelder, Martin P2-247
 Meyerovitch, Joseph Meyerovitch LB-5
 Miceli, Emanuela P1-428
 Michalacos, Stefanos P1-432, P1-96,
 P2-251, P3-126
 Michalak, Justyna P1-148, P2-278,
 P2-293, P2-36
 Michalakos, Stefanos P3-102
 Michalis, Lampros P1-54
 Michel, Peter FC9.6
 Michon, Jean P2-226
 Miettinen, Päivi T15
 Miettinen, Päivi J P1-88
 Miettinen, Päivi J. P1-395
 Mignot, Brigitte FC10.3, RFC2.2
 Mihova, Kalina P1-153, P1-307
 Mijatovic, Velja LB-12
 Mikhno, Hanna P2-111
 Miklosz, Agnieszka P1-421
 Miladinova, Daniela P3-307
 Milano, Giuseppe Maria P1-14
 Milczarek, Monika P2-93
 Milenkovic, Tatjana P1-10, P1-157,
 P1-167, P1-369, RFC10.1
 Miletta, Maria Consolata FC8.1
 Mille, Clémence RFC15.1
 Miller, Bradley P1-226
 Miller, Shahar RFC7.5
 Milliken, Brandon T. RFC4.6
 Mills, Kevin RFC11.3
 Milovanova, Natalia P1-206
 Milovanova, Natalya P1-69
 Mimouni Zerguini, Safia P2-280, P3-146
 Mimouni-Bloch, Aviva LB-5
 Mine, Yusuke P1-333
 Mingotti, Chiara P2-8
 Minutti, Carla P2-62, P3-251
 Mira, Marwa P1-320
 Miraglia del Giudice, Emanuele P1-93
 Miraglia del Giudice, Emanuele P1-111
 Miraglia del Giudice, Emanuele FC4.4,
 P1-354, P1-45
 Miraglia del Giudice, Emanuele RFC11.2
 Miranda Lora, América Liliana RFC1.3
 Miranda, Mirella C P1-10
 Miranda-Lora, América Liliana P1-15
 Mirante, Alice LB-16, P3-315
 Miras, Mirta P1-364
 Miras, Mirta P2-167
 Mitanchez, Delphine P1-303
 Mitrogiorgou, Marina P1-74, P2-214,
 P2-40, P3-190
 Mitrovic, Katarina P1-369
 Mittnacht, Jana P2-269
 Mittnacht, Janna P1-365
 Miyado, Mami FC3.1
 Miyoshi, Yoko P1-168, P1-243
 Mizuno, Haruo FC5.6, P3-173

- Mladenov, Vilchelm P2-174
 Mladenov, Vilhelm T13
 Mlodawska, Anna P2-286
 Mnif Feki, Mouna P2-266, P3-206, P3-216, P3-221, P3-25
 Mnif, Mouna P1-94, P2-39, P3-170, P3-229, P3-252, P3-97
 Mockeviciene, Giedre P2-70
 Modan-Moses, Dalit LB-25, RFC7.5
 Mogas, Eduard P2-164
 Mohamed Said Abugabal, Ahmed P2-11
 Mohamed, Shayma P3-160
 Mohamed, Yasmine P3-94
 Mohamed, Zainaba P1-286, P1-426
 Mohammed, Asmaa P1-141
 Mohammed, Idris P1-189
 Mohammed, Shayma P2-296, P3-153, P3-161
 Mohammedi, Fatiha P3-308, P3-331, P3-332
 Mohammedi, Fatiha P3-329
 Mohn, Angelika LB-13, P3-274, P3-314
 Mohnike, Klaus FC9.6, MTE 8, P1-10, P1-157, P1-167
 Mohnike, Konrad FC9.6
 Mohnike, Wolfgang FC9.6
 Mok, Elise P1-318
 Mol, Ben Willem LB-12
 Molagool, Sani P2-26
 Mondal, Sunetra P1-276
 Monica, Arancibia P2-46
 Monica, Mailat P3-114
 Moniez, Sophie P1-139
 Moniuszko, Marcin FC5.2
 Montalbano, Chiara P1-323, P1-428, P2-64, P3-115, P3-98
 Montanini, Luisa FC3.2
 Monteiro, Ana Cristina LB-16, P3-315
 Montenegro, Luciana P1-135, RFC8.2
 Montesinos-Costa, Mercè P1-193
 Montin, Davide P2-208
 Moon, Jung-Eun FC1.2, T14
 Moon, JungEun P3-305
 Moore, Rosario P2-46
 Mora, Cristina P2-145, RFC1.4
 Morabito, Letteria P1-346
 Morabito, Letteria Anna P1-300
 Moracas, Cristina P2-160
 Moraes Silva, Daniela P1-135
 Moraes, Daniela Rodrigues P1-270
 Morales Bazurto, Marjorie P1-410
 Morales, Cristobal P1-274
 Moramarco, Fulvio P3-287
 Moran, Carla MTE 2, P1-286, P1-426
 Morana, Giovanni P1-251, P1-252, RFC12.5
 Moreira, Ayrton RFC13.4
 Morel, Yves P1-296
 Morell, Lydia P1-192
 Moreno Morcillo, André P1-85
 Moreno, Jose Carlos P2-277
 Moreno, Luis P1-345, P3-119
 Moreno, Luis A. P1-33
 Moreno, Paula P2-277
 Moreno-González, Paula P3-116
 Morgan, Kate P1-205
 Morgan, Kate P3-266, RFC9.4
 Morillon, Paul RFC11.1
 Morin, Analia P1-8
 Morini, Giovanna P3-244
 Morioka, Ichiro P1-333
 Moriuchi, Hiroyuki FC3.4, P1-170
 Morkunaite, Ausra P2-70
 Moro, Mirella P1-120
 Morris, David E. P1-352
 Morris, Mavali P3-270
 Mortimer, Georgina L. FC1.5
 Mory, Adi P1-32
 Mosca, Fabio P2-298
 Moudiou, Tatiani P3-184
 Mouttalib, sofia P1-132
 Mouzaki, Konstantina FC7.1, P2-301
 Mowafy, Ehsan P3-70, P3-78
 Mroczek Wacinska, Joanna P2-134
 Muchantef, Karl RFC5.2
 Mughal, Zulf P1-172
 Muir, Tom RFC3.1
 Mukhwana, Ranson P3-290
 Mulder, Bjarne P1-377
 Mulder, Nicola P1-1
 Mullen, Mary P2-62
 Müller, Sven C S10.3
 Mulliqi Kotori, Vjosa P3-42
 Mulè, Flavia P2-192
 Mundekkadan, Shihab P1-189
 Munns, Craig RFC2.1
 Munyard, Paul P2-152
 Muratoglu Sahin, Nursel FC10.6
 Muratoglu Şahin, Nursel P1-342, P1-348, P3-180
 Muroya, Koji P1-243, P3-54
 Murray, Philip FC12.4, FC12.5, FC12.6
 Murtaza, Mohammed T19
 Murtezani, Avdi P3-284, P3-307
 Musa, Noha LB-17, LB-8
 Musa, Salwa P3-11
 Mushtaq, Talat P2-248, RFC14.4
 Muszynska, Kasia P1-327
 Mutlu Albayrak, Hatice P1-353
 Muz, Nataliia P3-262
 Muñoz, Maria Teresa RFC1.4
 Muñoz-Calvo, M^a Teresa P2-239
 Mysliwiec, Małgorzata P2-163, P3-66, P3-81
 Myśliwiec, Małgorzata P2-100, P3-163, P3-187
 MZ, Fuziah P2-292
 Mäestu, Evelin P1-17
 Mäkitie, Outi FC3.6
 Männistö, Jonna RFC15.4
 Mörse, Helena P1-419
 Müller, Hermann L. ERN1.1, P1-398, P1-99
 Mărginean, Otilia P2-116, P3-303
 McElreavey, Kenneth P2- 272
- N**
- N, Abo Khedr P3-70
 N.A, Fouzia P1-169
 Naafs, J.C. RFC9.2
 Nabil Khalaf, Amira P2-155, P3-79
 Nabila, Rekik P3-97
 Nada, Mona P2-120
 Nadia, Charfi P3-170, P3-97
 Nagaeva, Elena P1-356
 Nagamatsu, Fusa P1-416, P2-252, P3-54
 Nagano, Nobuhiko P3-282
 Naganuma, Junko P2-189
 Nagasaki, Keisuke FC3.1, P1-173, P1-243, P1-290, P2-249, P3-54
 Nagashima, Yuka P1-115
 Nagornaya, Irena P1-256
 Nagumo, Kiyoshi RFC3.4
 Naifar, Manel P3-206
 Naiki, Yasuhiro P1-406
 Nait Abdallah, Mohamed Said P3-189
 Najafli, Adam P1-390
 Naka, Katerina P1-54
 Nakamura, Akie P3-54, RFC12.3
 Nakano, Yukako P1-168
 Nakayama, Hirofumi P1-168
 Nakhla, Meranda P1-318
 Nakouti, Eleni P3-53
 Nalbantoglu, Ozlem P3-124, P3-2
 Nalbantoglu, Özlem P1-27, P2-12, P3-19, P3-233
 Nam, Hyo-Kyoung LB-15, P1-268, P2-283, P3-123
 Namba, Noriyuki RFC2.1, T16
 Nap, Annemieke LB-12
 Napoli, Flavia P1-251, P1-252, P1-391, P1-97, RFC12.5, RFC2.4, T3
 Naranjo Gonzalez, Cristina P2-102
 Nardini, Beatrice P2-232
 Narumi, Satoshi P1-115
 Nasedkina, Tatiana P2-109
 Navasardyan, Lusine P2-96, P3-289
 Nazarenko, Valeriya P1-328
 Nazim, Joanna P3-317
 Neagu, Nicolae P2-117
 Nedelea, Lavinia P1-202
 Nef, Serge FC10.2, FC10.3, P1-412, P2-271, RFC10.5
 Nelen, Willianne P1-377
 Neocleous, Vassos P1-334, P1-394, P2-275, RFC8.3
 Nessma Ourida, Taleb P1-292
 Netchine, Irene P1-218, P1-257
 Netchine, Irène FC12.1, LB-11, P1-80, RFC3.1, RFC8.2

- Netchine, Irène P1-303
 Netterlid, Axel P1-419
 Neuman, Vít P2-69
 Neumann, Uta P1-10, P1-156, P1-157, P1-167
 Nevoux, Jerome FC2.3
 Newbold, Sally P2-231
 Newnham, John T4
 Ng, Carolyn P1-65
 Ng, Sze May P2-88
 Ng, Nicholas Beng Hui P1-44, P2-16
 Ng, Nicholas BH P3-1
 Ng, Sze P1-288
 Ng, Sze May P1-314
 Ngoc Khanh, Nguyen P2-133, P3-141
 Nguyen Ngoc, Khanh P3-21, P3-260
 Nguyen Thu, Ha P3-21, P3-260
 Nguyen Trong, Thanh P3-21, P3-260
 Nguyen, Khoa Binh Minh P3-213
 Nguyen, Ngoc Khanh P2-7
 Nguyen, Thu Ha P2-7
 Ni, Jihong P2-81, P3-204
 Ni, Jinwen P3-197
 Ni, Yan RFC4.2
 Nicke, Lennart FC13.1
 Nicolaescu, Irina P3-39
 Nicolaides, Nicolas FC13.6
 Nicolardi, Francesca LB-18
 Nicolau, Belinda P1-197, P1-57
 Nicolescu, Ramona P1-70, P2-83, P3-194, P3-257
 Nicoll, Nicky P2-260
 Niechciał, Elżbieta P1-287
 Niedziela, Marek P3-46, RFC5.2
 Nielsen, Rasmus G P2-215, P3-29
 Nierop, Andreas RFC12.6
 Nierop, Andreas F.M. P1-250
 Nieschlag, Eberhard LB-3
 Nikaina, Eirini P1-118
 Nikankina, Larisa P1-165
 Nikitina, Irina P1-256
 Niklasson, Aimon P1-119, P1-250, P1-59, RFC12.6
 Niklińska, Wiesława p1-421
 Nilsson, Ola RFC2.1
 Nimri, Revital P2-267
 Nishi, Mirian Yumi P3-219
 Nishi, Mirian Yumie P1-270
 Nishijima, Keiji LB-1
 Nishimura, Naoko P3-69
 Nishioka, Junko P2-230
 Niu, Wenquan P3-272, P3-292
 Nişli, Kemal P1-236
 Njølstad, Pål Rasmus S9.1
 Noble, Janelle P3-87
 Nocon-Bohusz, Julita RFC12.2
 Noczynska, Anna RFC12.2
 Nogueiras, Rubén P1-345
 Noiszewska, Klaudyna P2-72
 Noordman, Iris P1-388
 Noorian, Shahab P3-328
 Noppe, Gerard RFC13.3
 Nordenström, Anna RFC3.1
 Noronha, Renata M RFC8.4
 Noufi- Barhoum, Marie P2-244
 Nourbakhsh, Mitra FC4.1, P1-341, P2-142
 Nourbakhsh, Mona FC4.1, P1-341, P2-142
 Novak, Daniel P1-22
 Noveski, Predrag P2-263
 Novina, Novina P3-300
 Nowaczyk, Jędrzej P3-130, P3-132
 Nuevo Casals, Silvia P2-127
 Numakura, Chikahiko P2-249
 Nunziata, Adriana P1-51
 Nuñez Chavarria, Eleonora P3-283
 Nyirimanzi, Naphtal P3-264
 Nyuzuki, Hiromi P2-249, P3-54
 Näke, Andrea P1-179
- O**
- O'Sullivan, Niamh P1-50
 Oakes, James A FC10.1, FC15.3
 Obara-Moszynska, Monika P3-46
 Obermannova, Barbora FC12.2, RFC14.2, RFC6.6
 Obermannová, Barbora P2-69
 Ocal, Isil P1-237
 Ochetti, Mariana P1-364
 Oehme, Ninnie P1-267
 Oehme, Ninnie B. P1-110
 Oehme, Ninnie HB P1-258
 Ogata, Tsutomu FC3.1, LB-1, RFC1.1, RFC12.3, T16
 Ogawa, Yohei P2-249, P3-54
 Ogawa, Yoshihisa LB-1
 Ogiwara, Yasuko P1-173
 Ogle, Graham P3-87
 Oguonu, Tagbo P2-199
 Oh, Arum P1-101, P2-209, P3-179
 Oh, Se-Young P1-431
 Oh, Seun P3-131
 Ohata, Yasuhisa P1-168, T16
 Ohlenschläger, Ute P1-51
 Ojeda, Ana P1-192
 Okada, Satoshi P1-243
 Okada, Tomoo P1-333
 Okminyan, Goar P1-147, P2-245, P2-261, P3-242, P3-253
 Okorokov, Pavel P1-357, P1-393, P1-405
 Okońska, Maja P3-163, P3-187
 Oksuz, Hale P1-117, P1-237
 Oksuz, Halil Ibrahim P1-237
 Okulov, Alexey P1-121, P2-245
 Okumura, Ryo P2-30
 Okure, Akanimo RFC3.1
 Olcese, Camilla P1-251
 Oleg, Latyshev P3-224
 Oleynik, Oxana P1-328
- Oliveira Santos, Allan P1-85
 Oliver, Isabelle P1-139, P1-150
 Olivieri, Antonella P1-423
 Olszanecka-Glinianowicz, Magdalena P1-41
 Olukade, Tawa P2-71, P2-98
 Olukman, Özgür LB-14
 Omar, Magdy P3-73
 Omar, Omneya M P2-120
 Omar, Omneya Magdy FC4.5, P2-33, P3-41
 Omar, Tarek P2-258
 Ön, Şebnem P1-285
 Onal, Hasan P1-159, P1-162, P1-248
 Onal, Hasan P1-283
 Onay, Hüseyin P3-217, RFC6.4
 Oneto, Adriana P2-228
 Ongen, Yasemin Denkboy P1-329
 Ooi, Delicia SQ P2-16
 Oprandi, Daniela P2-8
 Orbach, Daniel P2-226
 Orbak, Recep P2-28, P2-42
 Orbak, Zerrin LB-2, LB-6, P1-81, P2-28, P2-42, P3-61
 Oren, Asaf P1-265, P1-397, P2-1
 Orenstein, Naama P2-267
 Orimo, Hideo RFC6.5
 Orlova, Elizaveta P1-165, P2-212
 Oron, Tal T17
 Orozco Morales, Jose Antonio RFC1.3
 Ortiz-Cabrera, Nelmar Valentina P1-376
 Ortolano, Rita P1-300, P2-227
 Oryan, Tal P1-288
 Osman Ahmed, Shayma P3-165
 Osman, Engy P3-140
 Osokina, Irina P1-144, P1-315, P3-47, P3-58, P3-75
 Osredkar, Damjan RFC3.6
 Ostrow, Vlad P1-226
 Osuji, Oliver P2-67
 Ota, Sho P1-235, P1-84
 Otfried Schwab, Karl P2-178
 Otonkoski, Timo RFC15.4
 Otte, Trui P2-136
 Otten, Barto RFC2.5
 Ottolenghi, Chris LB-11
 Otçu Temur, Hafize P1-396
 Ou, Hui P1-182, P3-89
 Ou, Hui P1-232
 Ou, Hui P2-68
 Ouarezki, Medical/Health P3-113
 Oulas, Anastasios P1-394, P2-275
 Ould Mohand, Ouamer P3-176, P3-201
 Ouyang, Qian P2-177
 Özalkak, Servan P1-160, P1-330, P1-342, P1-348, P2-119, P2-234, P3-225
 Özalp Kızılıy, Deniz LB-14, P3-268, P3-285
 Ozay, Mustafa P3-61
 Özbaran, Nazlı Burcu P3-217

Ozbek, Mehmet Nuri P1-91
Ozbek, Mehmet Nuri P1-207, P1-254, RFC8.5
Özcabı, Bahar P1-48, P2-137
Özcan, Alper P1-244
Özdoğan, Özhan P2-284
Ozdemir, Taha Resid P1-245, P2-12, P3-2
Ozden, Ayse P2-42, P3-235, P3-61
Özek, Gülcihan P1-414
Ozen, Ahmet P1-116
Özen, Samim P1-414, P3-217, RFC6.4
Özer, Erdener P2-284
Özer Kaya, Özge P1-308
Özgen, İlker Tolga P1-396
Ozgurhan, Gamze P2-51
Özkan, Yekta P3-285
Ozkan, Behzat P1-27, P2-12, P3-2, P3-19, P3-124, P3-233
Ozkaya, Beyhan P1-27, P2-12, P3-2, P3-19, P3-124, P3-233
Özkinay, Ferda P3-217, RFC6.4
Ozon, Alev P1-239
Ozon, Z. Alev P1-404, P2-223, P2-224
Ozono, Keiichi LB-1, P1-168, P1-243
Ozpak, Lutfiye P1-237
Ozsü, Elif FC6.4, P3-8, RFC8.5
Ozturk, Ayse Pinar P1-145, P2-45, P2-195, P2-270
Öztürk, Hasan Serdar P1-160, P2-119, P3-225
Ozturk, Nurinnisa LB-2, LB-6, P3-61
Öztürk, Yeşim P1-285
Öztürkmen Akay, Hatice P1-48
Özyurt, Gonca P1-335
Özyurt, Jale P1-99
Özyilmaz, Berk P3-106

P

P.C. Bezerra, Marilia P1-39
Pachajoa, Harry P3-186
Padidela, Raja FC2.1, FC2.2, P1-172, RFC2.1
Paetow, Ulrich P1-51
Pagliazzzi, Angelica P1-194, P1-336, P1-362, P2-181
Pajno, Roberta P3-144, P3-205
Paketçi, Ahu P1-28, P2-284, P3-198, P3-250
Pakhomova, Viktoria P3-262
Palazzo, Viviana P1-194, P1-336
Palenzuela Revuelta, Inmaculada P2-102
Palenzuela, Inmaculada P2-74
Palma, Antonio P1-392, P1-95
Palma, Laura P1-5
Pancheva, Ruzha P1-350
Pandey, Amit V FC3.3, RFC13.6
Pandey, Amit V. RFC15.3
Panebianco, Valeria P3-5
Pani, Fabiana P1-251
Panic, Sanja P1-369

Panichev, Oleksandr P2-299
Pankratova, Maria P1-393, P2-201
Panou, Evangelia P3-181
Pantaleo, Marilena P1-194, P1-336, P2-181
Pantelidou, Maria P1-334
Paone, Laura P1-14
Papachatzi, Eleni P3-68
Papadimitriou, Anastasios P1-16
Papadimitriou, Dimitrios T. P1-16, P3-301
Papadopoulou, Marina P3-96
Papadopoulou-Legbelou, Kyriaki P2-301
Papaevangelou, Vassiliki P1-74, P2-40, P3-190
Papafakis, Michail P1-54
Papaioannou, Nikoletta RFC8.3
Papale, Mariella P2-75
Papendieck, Patricia P1-152
Paperna, Tamar P1-32
Paradis, Gilles P1-197, P1-57
Paramasivam, Nagarajan FC5.5
Parastatidou, Stavroula P3-236
Parent, Anne-Simone P3-254
Parias, Rodrigo P1-240
Parish, Anthony P2-62
Parisi, Giuseppe P2-75
Park, Hyesook P1-40
Park, Hyojung P2-158, P2-282
Park, Julie P1-246
Park, Kyung Hee P1-429
Park, Mi Jung P1-203, P2-158
Park, Na Ri P1-368
Park, Yong Hoon P3-15
Park, Young Joo FC5.3
Parlayan, Cüneyd P1-145
Parodi, Stefano T3
Parpagnoli, Maria P1-106, P1-401, P2-171, P2-232, RFC11.2
Partenope, Cristina P1-401, P3-144, P3-205
Partsalaki, Ioanna P3-48
Parween, Shaheena FC3.3, RFC15.3
Pascanu, Ionela P2-117
Pascanu, Maria-Ionela P1-358
Paschke, Ralf P1-148
Pasqualini, Titania P2-167
Pasquarelli, Serena P3-274
Passanisi, Stefano P2-147, P2-186
Pastrak, Aleksandra P1-361
Pasztak-Ogilka, Agnieszka P1-131
Patel, Kajal FC12.5
Patel, Leena P1-6, RFC13.2
Patel, Riddhi P2-73, P3-227
Patera, Patrizia FC7.3
Patil, Srinivas P1-280
Patrascu, Irina P3-39
Patricelli, Maria Grazia P1-420
Patsatsia, Ekaterine P1-151
Patsch, Janina FC2.4

Patti, Giuseppa P1-391, RFC12.5, T3
Patti, Giuseppa P1-97
Patócs, Attila RFC3.1
Paul, Praveen George P2-79
Paula, Tatiana Evelin P1-270
Paulsen, Anne RFC3.2
Pautasso, Valentina LB-4
Pauwels, Christian P2-226
Pavlyshyn, Halyna P2-299
Pałasz, Artur P3-275
Pearce, Simon FC5.1
Pedicelli, Stefania P1-106, P1-386, P1-401, P3-17
Pedulla', Marcella FC4.4, P1-45
Peek, Ron P1-377, RFC12.1
Peet, Aleksandr P1-289
Peeters, Robin P. P1-367
Pei, Zhou P2-95, P3-24, RFC1.2
Pei, Zhou P1-186
Pei, Zhou RFC4.5
Peleg, Amir P3-281
Pelizzo, Gloria P1-323
Pellegrin, Maria Chiara LB-18, P1-360, P3-168
Pellikaan, Karlijn FC8.3, P1-367
Peluso, Francesca P1-194, P1-336, P1-362, P2-181
Pena, Alexia P1-190
Pena, Fernanda P1-228
Pena-León, Verónica P1-345
Peng, Megan P1-327
Peng, Ya-guang P3-145
Peng, Ye P1-49
Penke, Melanie P1-30
Pennell, Craig T4
Penninger, Josef PL1
Pennisi, Patricia FC14.1, P1-359
Pepe, Giorgia P1-346, P1-422, RFC5.1
Peppa, Melpomeni P1-74, P2-40
Perafan, Lina P3-186
Pereira, Alberto RFC3.1
Pereira, Ana P1-399
Pereira, Carla LB-16, P3-315
Pereira, Catarina P2-51
Perez Cuevas, Isabel P3-101
Perez de Nanclares, Guiomar FC6.6
Perez garrido, Natalia P1-129
Perez Garrido, Natalia P2-259
Perez, Viviana P1-37
Peri, Alessandro P1-97
Perin, Laurence LB-11
Perl, Liat P1-265
Perlman, Shira P1-128
Perri, Annamaria P1-378, P2-182, P3-164
Perrot, Valérie P1-212, P1-214
Perrotta, Silverio P1-97, RFC11.2
Perrotti, Chiara P2-8
Perry, Rebecca P1-9
Persani, Luca P1-120, P1-420, RFC3.1
Perçin, Ferda P1-103, P1-351

- Peskavaya, Nadzeya P1-230
 Peterkova, Valentina P1-165, P1-356, P2-212, P2-9
 Peters, Catherine RFC5.4
 Peterson, Pärt S8.1
 Petkovic, Grace P2-180
 Petraitiene, Indre LB-9
 Petrou, Vassilios P1-432
 Petrov, Michael P2-35
 Petrov, Vasilij P2-35
 Petrov, Vasiliy P1-415, P1-55, P2-250
 Petrov, Vasily FC11.4, P1-332
 Petrova, Chaika P2-173
 Petrova, Ekaterina P3-177
 Petrova, Irina P1-78, P2-185
 Petruzelkova, Lenka FC12.2
 Petruželková, Lenka P2-69
 Petryk, Anna P1-21
 Peycelon, Mathieu FC10.3
 Peña, Sonia P2-90
 Pfeiffer, Kathryn M. P1-235
 Pfeiffer, Kathryn M. P1-84
 Pfister, Marc FC7.2
 Pfäffle, Roland P1-227
 Phan-Hug, Franziska P2-264
 Philip Banoub, Veronia RFC1.6
 Phillip, Moshe P1-109, P1-187, P1-291, P2-115, P2-267, T17
 Phuong Thao, Bui P2-133, P3-141
 Phylactou, Leonidas RFC8.3
 Phylactou, Leonidas A P1-334, P1-394, P2-275
 Piacente, Laura RFC6.2
 Piatelli, Gianluca P1-391
 Pie Juste, Juan P1-229
 Pienkowski, Catherine P1-132, P1-139, T8
 Pietropoli, Alberto P1-226
 Pietschmann, Peter FC2.4
 Piketty, Marie LB-11, P2-176
 Piketty, Marie P3-238
 Pilotta, Alba P2-8
 Pin, Jacopo Norberto P3-295
 Pineau, Jean Claude P2-176
 Pinhas-Hamiel, Orit FC1.6, P2-123, RFC5.5, RFC7.5
 Pino, Jesus P2-61
 Pinon, Michele P2-208
 Pinto, Graziella P1-80, P2-176, P2-226
 Pinto, Renata P2-57
 Pinto, Renata Machado P2-196
 Pintos, Carla P2-279
 Pirgon, Özgür P2-268, P2-291
 Pisareva, Elena P3-166
 Pistorio, Angela P1-251
 Pitea, Marco P3-144, P3-205
 Pitoia, Fabian LB-26
 Pivko-Levy, Dikla RFC7.5
 Pizer, Barry P1-259
 Pizzul, Mariagrazia P1-360
- Piłaciński, Stanisław P1-287
 Plachy, Lukas FC12.2, RFC14.2, RFC6.6
 Placzkowska, Sylwia LB-19
 Plamper, Michaela P1-234
 Plaseska-Karanfilska, Dijana P2-263
 Podchininenova, Dariya P1-328
 Pogadayeva, Nataliya P3-237
 Poggi, Helena P2-46
 Pogoda, Tatyana P1-55
 Pohl, Fabian P1-398
 Pohlenz, Joachim FC5.5, P3-258
 Poitou, Christine S1.3
 Polak, Agnieszka T5
 Polak, Michel FC5.4, P1-212, P1-214, P1-226, P1-80, P2-176, P2-226
 Polak, Michel P3-238
 Polat, Zeliha Başak LB-2
 Polidori, Nella LB-13, P3-314
 Polnik, Dariusz p1-421
 Poluzzi, Francesca P1-417
 Pombo, Manuel P2-61
 Pongratnakul, Sarunyu P1-201
 Pons, Roser P3-302
 Pontoizeau, Clément LB-11
 Poomthavorn, Preamrudee P1-201, P2-131, P2-26
 Poon, Grace WK P3-100
 Poon, Sarah WY P3-100
 Pop, Raluca P1-358
 Pop, Raluca-Monica P2-117
 Popova, Ralitsa P1-350
 Porcar Cardona, Ines P3-293
 Porquet-Bordes, Valerie P3-33
 Porta, Gilda P1-199
 Portale, Anthony A. FC2.1, FC2.2, RFC2.1
 Portela, Maite LB-12
 Porter, John P1-156
 Portillo, Maria Puy P3-320
 Ports, Emilia P1-190
 Posey, Jennifer Ellen P1-273
 Pott Godoy, Clara P2-90
 Pouker, Iulia P3-281
 Powell, Michael P2-293
 Poyrazoglu, Sukran P1-134, P1-306, P2-270, P2-45
 Poyrazoglu, Sükran P2-137
 Poyrazoğlu, Şükran P1-145, P1-236, P1-262, P1-390, P2-195
 Pozas Mariscal, Sara P2-102
 Pozo, Jesús P1-100
 Pozo-Román, Jesús P1-376
 Pozzessere, Anna P2-21
 Pozzobon, Gabriella P1-106, P1-401, P2-232
 Pozzobon, Gabriella Cinzia P3-144, P3-205
 Požgaj Šepc, Marija P3-231
 Prada, Silvina P1-410
 Pramanik, subhodip P1-276
- Pramatarova, Tania P1-307
 Prampolini, Beatrice P1-185
 Prandstraller, Daniela P1-378
 Prasad, R RFC13.5
 Prasad, Rathi FC13.5
 Prathivadi Bhayankaram, Nuthana P2-97
 Prats-Puig, Anna P1-56, RFC4.3
 Predieri, Barbara P1-185, P1-417, RFC14.3, RFC3.5, RFC7.6, RFC9.6, T6
 Prematilake, Dilusha P2-80, P3-291, P3-304, P3-322
 Pribilincova, Zuzana P2-168
 Prieto Velhote, Manoel Carlos P1-199, P1-39
 Prinz, Nicole P1-179
 Prisacari, Alina P3-39
 Prié, Dominique FC2.3, P1-23
 Prochazka, Martin LB-27
 Profant, Milan P2-91
 Provenzano, Aldesia P1-194, P1-336, P2-181
 Pruhova, Stepanka FC12.2, P1-317, RFC14.2, RFC6.6
 Průhová, Štepánka P2-63
 Průhová, Štěpánka P2-69
 Pu, Ronghui P3-44
 Puel, Olivier P1-408
 Puerto-Carranza, Elsa P2-127
 Puget, Stéphanie P2-226
 Pugliese, Marisa P1-68, RFC7.6, RFC9.6
 Pulungan, Aman P3-300
 Purge, Priit P1-17
 Purushothaman, Preetha FC9.1, P1-311
 Puthi, Vijith P1-104
 Puñales, Marcia P3-40
 Puñales, Márcia P3-35
 Pykov, Mihail P1-147
 Pyra, Eileen P1-9
 Pyrzak, Beata P1-73
 Pérez Candás, José Ignacio P1-272
 Pérez, Jacobo P1-382
 Pérez-Jurado, Luis A. P1-100
 Pérez-Segura, Pilar P2-23, P3-99
- Q**
 Qing, Yanrong P1-277
 Quaglietta, Lucia RFC11.2
 Quartararo, Maria P1-299
 Qudah, Mansour P2-67
 Qudaisat, Anwar P2-193
 Quinton, Richard FC15.1
 Quitter, Friederike P2-205
 Quraan, Eyad P2-193
 Qureshi, Abid Ali P3-310
- R**
 Rabenstein, Hannah P1-51
 Rabie, Walaa P1-141
 Rachid, Ludmilla P1-39
 Rachmiel, Mariana P1-397

- Rade, Vukovic P1-369
 Radetti, Giorgio P3-267
 Radi, Alin P1-295
 Radovick, Sally FC15.1
 Raducanu-Lichiardopol, Corina P1-167
 Raftopoulou, Sofia FC13.6
 Raghupathy, Palany P1-312
 Rahme, Elham P1-318
 Raile, Klemens FC15.2
 Raimann, Adalbe P1-76
 Raimann, Adalbert FC2.4, FC6.2, RFC15.5
 Raiola, Giuseppe P2-300
 Raivio, Taneli P1-395, P1-88, S5.3, T15
 Raivo, Joose RFC15.4
 Raj, Meena P1-215
 Raj, Viralsinh P3-85
 Rajanayagam, Odelia P1-286
 Rakhimberdiyeva, Ziyoda P3-49
 Rakhimova, Gulnara P2-295, P2-89, P3-112
 Rakhimova, Gulnara P1-325
 Ramachandran, Smita P2-94
 Ramachandran, Smita P2-206
 Ramadan, Magdy P2-11
 Ramakrishnan, Renuka P1-102, P2-190
 Ramirez, Joaquín RFC1.4
 Ramirez, Pablo P1-129
 Ramirez, Pablo P2-259
 Ramon-Krauel, Marta FC15.5
 Ramos Fuentes, Feliciano P1-229
 Ramzy, Heba P3-78
 Ramzy, Tarek LB-17
 Randell, Tabitha P1-172, P1-352, P1-384, P1-6, P3-155, RFC13.2
 Ranke, Michael B RFC2.3
 Rankova, Kamelia P2-174
 Rapini, Novella FC7.3
 Rappold, Gudrun S5.2
 Rappold, Gudrun A. FC5.5
 Rasmussen, Michael H P1-363
 Rasmussen, Michael Højby FC14.5
 Rassas, Ahmed P2-60
 Rath, Shoshana P3-200
 Ratnasabapathy, Piriya P1-424
 Rauch, Frank RFC6.3, S2.2
 Raum, Kay FC2.4
 Rausin, Leon P1-70
 Ravagnini, Gloria RFC14.3
 Ravikulan, Abhimati P1-312
 Raygorodskaya, Nadezda P1-133
 Razanskaite-Virbickiene, Dovile P2-70
 Razzaghy Azar, Maryam FC4.1, P1-341, P2-142
 Reales-Arroyo, Ana Maria P2-118
 Redway, Martha FC9.5
 Rees Smith, Bernard P2-36
 Regalbuto, Corrado P1-323, P1-428, P2-64, P3-115, P3-98
 Rehberg, Mirko T18
 Reho, Paolo P1-194, P1-336
 Reina-Ceballos, Inmaculada P2-118
 Reinauer, Christina P2-20
 Reinehr, Thomas P1-231, P1-379, P1-380
 Reinl, Erin S10.1
 Reinoso, Andrea P1-8
 Reisch, Nicole FC13.1, P1-269, RFC3.1
 Reish, Nicole T8
 Rekik, Nabila P2-266, P2-39, P3-170, P3-221, P3-25, P3-252
 Rekik, nabila P3-216
 Rekler, Dina RFC10.6
 Remesar, Xavier RFC4.3
 Remmel, Liina P1-17
 Renbaum, Paul P1-128
 Renbaum, Pinchas FC11.3
 Renggli, Luzia FC7.2
 Rentsch, Katharina FC7.2
 Requejo, Flavio P1-249
 Reschke, Felix P1-66
 Restrepo, Manuela P2-159
 Reszec, Joanna p1-421
 Revenco, Ninel P1-108
 Rey, Rodolfo LB-7, P1-167, P1-262, RFC10.1
 Rey, Rodolfo A. P1-410
 Reynaud, Rachel P3-269
 Rhie, Seonkyeong P2-78
 Rhie, Young-Jun LB-15, LB-23, P1-268, P2-283, P3-123
 Rho, Jung Gi P1-138
 Riani, Marco P2-150, P3-133
 Riaño-Galan, Isolina FC6.6
 Riaño-Galán, Isolina P1-272
 Ribeiro, Sablony Carreiro P1-155
 Rica, Itxaso P2-254, P2-279
 Ricci, Franco P1-107, P1-362
 Richards, Brent RFC6.3
 Richter, Sandy P1-30
 Richter-Unruh, Annette P1-269
 Riddle, Miles P2-97
 Riedl, Stefan P1-261, P1-271, P2-247
 Riello, Francesca LB-22
 Riera, Elena P1-56
 Righi, Beatrice P1-185, RFC3.5
 Riquelme, Joel P1-228
 Risso, Mariana P2-297
 Rittig, Søren P1-136
 Ritzén, Martin P2-162
 Riu, Carmen P2-228
 Rivarola, Marco Aurelio P1-129, P2-259
 Rivera, Josefa P1-382
 Rivera, Patricia FC14.3, RFC14.1
 Rizzoli, Christian RFC9.3
 Rizzoti, Karine FC11.2
 Rizzotto, Marcia Ines Boff P1-155
 Robalo, Brígida P1-253
 Robert, Annie T9
 Roberts, Mary Scott FC2.1, FC2.2
 Robinson, Lindsay P1-352
- Robinson, Louise RFC11.1
 Robinson, Sylvia P3-251, P3-52
 Roca Portella, Berta P2-127
 Roca, Fernanda P1-82
 Rocha Franco, Ruth P1-199, P1-39
 Roche, Edna RFC14.5
 Roche, Katherine W. FC15.1
 Roco-Rosa, María P3-306
 Roda, Célina LB-11
 Rodari, Giulia P1-98
 Rodie, Martina P1-266
 Rodrigue, Danielle P1-213
 Rodrigues, Daniela Moraes P3-219
 Rodriguez, Amparo RFC1.4
 Rodríguez Castaño, Patricia RFC13.6
 Rodríguez de Fonseca, Fernando FC14.3, RFC14.1
 Rodríguez Gutiérrez, Daniel FC10.2, FC10.5
 Rodríguez, Amaia P2-254, P2-279
 Rodríguez, María Eugenia P1-72
 Roelants, Mathieu P1-110, P1-258, P1-267
 Roeper, Marcia P1-204
 Roest, Inez LB-12
 Roeth, Ralph FC5.5
 Rogova, Olga P1-147
 Rogowicz-Frontczak, Anita P1-287
 Rohayem, Julia LB-3, MTE4
 Rohrer, Tilman R P1-226
 Roia, Anna P3-244
 Rojas Gil, Andrea Paola P3-48
 Rojas Velazquez, Maria Natalia FC3.3
 Rojas-Gil, Andrea-Paola P3-68
 Rojek, Aleksandra P3-46
 Rojnic Putarek, Natasa P1-36
 Roka, Kleoniki P3-302
 Romano, Silvia P3-43
 Romanová, Martina P2-69
 Rombauts, Luk P1-124
 Romero de Ávila Montoya, José Mario P1-229
 Romero, M del Mar P1-331
 Romero-Nava, Rodrigo P1-43
 Ron, Idit FC1.6
 Rooman, Raoul P2-153
 Ropelato, María Gabriela LB-7, P1-410, P1-72
 Roper, Marcia P2-144
 Ros, Purificación FC8.2, FC8.4
 Ros-Pérez, Purificación P3-276
 Roschger, Paul FC6.1, RFC15.5
 Rose, Steven J RFC14.4
 Rosenberg, Anna FC8.3
 Rosendahl, Karen P1-110, P1-258
 Rosenfeld, Ron P1-365
 Rosenfeld, Ron G. P1-361
 Rosolowsky, Elizabeth P1-427, P3-234
 Ross, Judith P1-226

- Ross, Richard P1-10, P1-156, P1-167, RFC10.1
- Rossi, Andrea RFC12.5
- Rossi, Stefano P2-8
- Rossignol, Sylvie FC12.1
- Roswall, Josefina P1-195
- Roth, Christian L. FC4.6, RFC4.6
- Rothbuhler, Anya P1-213
- Rothenbuhler, Anya FC2.3, FC6.6, P1-18, P1-23, RFC2.2
- Rothermel, Juliane P1-231, P1-380
- Rotolo, Novella P2-75
- Rotondi, Daniela P1-423
- Rotteveel, Joost FC13.2, FC13.4, RFC11.6
- Roucher-Boulez, Florence P1-296
- Rouf, Siham P3-142, P3-147, P3-148, P3-86
- Rouga, Elena P3-53
- Roujeau, Thomas P2-226
- Roviglione, Barbara P1-252
- Rowland, Maya FC4.6
- Rozenkova, Klara P1-317
- Rubio, Leticia FC14.3
- Rubstein, Adrian P1-82
- Rudkova, Ekaterina P2-172
- Ruggiero, Jessica P2-8
- Rugilo, Carlos P1-249
- Ruibal, Gabriela P3-283
- Ruiz, Miguel Angel Maese LB-20
- Ruiz-Babot, Gerard FC15.4
- Ruiz-Piñon, Manuel P1-345
- Rumie, Karime P1-37
- Rumińska, Małgorzata P1-73
- Rumyantsev, Alexander P2-109
- Rupérez, Azahara I. P1-33
- Rush, Eric T. P1-21
- Rushworth, R. Louise P1-299
- Russo, Gianni P1-300
- Ruszała, Anna P3-279
- Rutges, Joost P3-178
- Rutigliano, Irene P1-401
- Ryan, Fiona P1-6, RFC13.2
- Rybka, Olena P3-121
- Rydzewska, Marta P2-293
- Ryzhova, Marina FC11.4
- S**
- S Mohamed, Rabie P3-152
- S. Bruserud, Ingvild P1-110
- Saafi, Wiem P3-25
- Saare, Liisa P1-289
- Saatov, Talat P1-325
- Sabir, Hemmen P1-204, P2-144
- Sabry, Aly RFC7.3
- Sabt, Aml P1-313, P2-183
- Sachdev, Pooja P1-384, P3-155
- Sadikova, Akidahon P2-89
- Saelens, Brian FC4.6
- Saenger, Paul FC14.5
- Saengkaew, Tansit FC15.4
- Saenz-Lussagnet, Juan Manuel P2-118
- Saffari, Fatemeh P1-24
- Safi, Wajdi P1-94, P2-39, P3-170, P3-206, P3-221, P3-229, P3-25, P3-252, P3-97
- Safi, Wajdi P3-216
- Safi, wajdi P2-266
- Sagen, Jørn P1-267
- Sagi, Liora P1-347
- Sagi-Dain, Lena P3-281
- Sagiroglu, Mahmut Samil P1-3
- Sagmeister, Susane FC6.2
- Sagmeister, Susanne P1-76
- Şahin, Süleyman P2-255
- Sahlin, Lena P1-42
- Sai, Shuji P2-30, RFC3.4
- Said Seleem, Wail P3-152
- Saiki, Reo P2-230
- Sainte-Rose, Christian P2-226
- Sainz Costa, Talia P1-374
- Saito, Emiko P1-333
- Saito, Shihō RFC6.5
- Saito-Hakoda, Akiko P2-285
- Saitoh, Akihiko P3-54
- Saitoh, Shinji FC5.6, P3-173
- Saitsu, Hirotomo FC3.1, T16
- Saka Güvenç, Merve P3-226
- Sakher, Samia P3-146
- Sakka, Sophia P3-270, P3-327
- Sakremath, Rajesh P1-286
- Salah, Shimaa P1-34
- Salama, Husam P2-71, P2-98
- Salamanca, Luis P2-145, RFC1.4
- Saleh Elsayed, Salma Mohamed P2-50
- Saleh, Hani P3-45
- Salerno, Maria Carolina P1-300, P1-97
- Salerno, Mariacarolina HDI 1.1, P1-106, P1-111, P1-120, P1-409, P1-422, P2-160, P2-171, P2-232
- Sales De Gauzy, Jerome P3-33
- Salimi Dafsari, Roschan P1-204, P2-144
- Sallai, Agnes FC10.3
- Salles, Jean Pierre P3-33
- Salles, Jean-Pierre P1-139, RFC2.2, T8
- Salonen, Anne T15
- Salum D'Alessandro, Marcela P1-199
- Samara-Boustani, Dinane P1-80, P2-176, P2-226
- Samira, Aggoune P1-292, P2-161
- Samoilova, Juliya P1-328
- Samsonova, Lubov P2-245, P2-261, P3-242
- Samsonova, Lyubov P1-147, P3-253
- Samuels, Mark E. FC5.4
- San Martin, Javier FC2.1, FC2.2, RFC2.1
- Sanchez Escudero, Veronica P2-128
- Sanchez Salado, Laura P2-128
- Sanchez-Laguna, Francisco P1-331
- Sandamal, Sajith P2-290
- Sandberg, David P1-125
- Sanderson, Elaine P1-35
- Sandra, Tilitzky P1-240
- Sandrikova, Vilja P2-168
- Sandy, Jessica P1-177, P3-270, P3-327
- Sangun, Levent P1-237
- Sani, Ilaria P1-194, P1-336, P2-181
- Sannikova, Ekate P2-245
- Sannikova, Ekaterina P3-242
- Santamaria, Fabiana P1-409
- Santi, Maristella P3-83
- Santoro, Claudia RFC11.2
- Santos, Rui P1-172, P3-270
- Santos-Silva, Rita P2-14, P2-4
- Santucci, Simona P2-182, P3-164
- Sanzone, María P1-410
- Saracco, Luca P1-420, P2-298
- Saraff, Vrinda P1-426, RFC6.5
- Sarafoglou, Kyriakie RFC13.1
- Sarasua, Ainhoa P2-279
- Sarasua-Miranda, Ainhoa P3-316, P3-320, P3-333
- Saraswathi, Saras P1-189
- Sartori, Chiara FC3.2, RFC14.3
- Sartorio, Alessandro P3-267
- Sarvasiddhi, Satish P3-299
- Sarıkaya, Emre P3-263
- Sas, Theo RFC2.5
- Sasaki, Goro FC3.1, P2-217
- Sato, Cleber P2-194
- Sato, Hiroyuki P1-416, P2-252
- Sato, Seiji P2-217
- Sato, Takeshi P1-115
- Sato, Yasuhiro T16
- Satoh, Mari P1-290
- Sauna, Alessandra P1-247, P2-75, P3-5
- Savage, Martin O RFC14.4
- Savagner, Frédérique P1-150
- Savagner, Frédérique LB-4
- savas erdeve, senay FC10.6
- Savas Erdeve, Şenay P2-119
- Savas-Eerdeve, Senay P1-181
- Savateev, Alexandre FC11.5
- Savaş Erdeve, Şenay P1-284, P1-330, P1-348, P2-198, P2-234, P3-180
- Savchuk, Iuliia P1-42
- Saveanu, Alexandru P3-269
- Savilahti, Erkki T15
- Sawada, Hirotake P1-290
- Sawano, Kentaro P3-54
- Sawicka, Beata P1-148, P2-278, P2-36, P3-167, T2
- Sayarifard, Azadeh P1-146
- Sayarifard, Fatemeh P1-146
- Scaglia, Paula Alejandra P1-72
- Scarano, Emanuela P1-378, P2-182, P3-164
- Schachter-Davidov, Anita P1-397, P2-1, P2-6
- Schanze, André FC13.1
- Schawrz, Wendy P1-9
- Schebek, Martin P1-211

- Schevchenko, Iryna P2- 272, P2-281, P3-237
- Schiaffini, Riccardo FC7.3
- Schiffer, Lina RFC13.2
- Schipper, Saskia P1-92
- Schirmer, Melanie P1-51
- Schiza, Melpo P1-394
- Schleedoorn, Myra P1-377, RFC12.1
- Schlesner, Matthias FC5.5
- Schlingmann, Karl Peter P2-53
- Schnect, Francis P1-142
- Schneider, Johannes FC2.4
- Schoenmakers, Nadia RFC5.5
- Schou, Anders J P3-29
- Schreiner, Felix FC9.4, P1-234
- Schubert, Tina FC13.1
- Schuhmann, Martin P1-398
- Schulte, Sandra FC9.4
- Schulze, Egbert P3-4
- Schur, Ellen A. FC4.6
- Schwab, Karl Otfried FC7.6, P2-32
- Schwandt, Anke P1-179
- Schweizer, Roland FC6.5
- Schwitzgebel, Valerie P2-70
- Schwitzgebel, Valérie P3-84
- Schwitzgebel, Valérie M. P2-264
- Schönau, Eckhard T18
- Schørring, Mia E. P1-136
- Scianguetta, Saverio P1-97
- Scilipoti, Martina RFC11.2
- Scott, Frank S1.2
- Scrinic, Olesea P2-207
- Scurry, Bonnie P1-65
- Sebar, Khadidja P3-176, P3-201
- Sebastian, Brenner P1-66
- Segel, Reeval P1-128
- Segev-Becker, Anat P1-265, P2-1, P2-6
- Seghaye, Marie-Christine P3-254
- Seifert, Monika RFC12.2
- Seila, Ibadula P2-207
- Sekler, Opal P2-6
- Selim, Nihad P3-189, P3-330
- Sellers, Robert FC12.4, FC12.5, FC12.6
- Selveindran, Nalini P1-403
- Seminara, Stephanie B. FC15.1
- Semler, Jörg T18
- Semple, Claire P2-108, P3-104
- Semple, Robert P3-266
- Semrouni, Mourad P3-146
- Sen, Askin P3-36
- Şen, Semra P3-285
- Senniappan, Senthil FC9.2, P1-102, P1-113, P2-180, P2-190, P2-236
- Seo, Ji-Young P3-88
- Seo, Moon Young P1-203
- Seoane, Luisa M. P1-345
- Sequera, Ana P3-283
- Serdaroğlu, Ayşe P2-103
- Serebryakova, Elena P3-150
- Sert, Caroline P1-212, P1-214
- Sert, Tuğba P1-294
- Sertedaki, Amalia FC1.3
- Sertedaki, Amalia P1-118
- Servello, Raffaella P1-360
- Sethi, Aashish FC9.2, P1-102, P1-259, P2-180
- Setoh, Johnson W.S. P1-67
- Seven Menevse, Tuba P1-175, P1-176, P3-202
- Seven Menevse, Tuba P2-52
- Seven, Tuba P1-402
- Severino, Maria Savina RFC12.5
- Severino, Mariasavina P1-391
- Sezer, Abdullah P1-351
- Sfakiotaki, Maria P3-192
- Shaalan, Yomna P2-87
- Shaat, Mona P1-381, P2-193, P3-28
- Shackleton, Cedric H.L. P1-162
- Shafik Nada, Ahmed RFC1.6
- Shagazatova, Barno P3-49
- Shah, Pratik P1-205
- Shah, Pratik P2-143, P3-266, RFC5.4, RFC9.4, RFC9.5
- Shah-Kulkarni, Surabhi P1-40
- Shahroor, Sarit P3-16
- Shaikh, M Guftar RFC2.6
- Shaikh, M. Guftar P1-125
- Shalitin, Shlomit P1-187, P2-115, T17
- Shamansurova, Zulaykho P1-325
- Shangguan, Huakun P2-177
- Sharaf, Muna FC11.3, P1-128
- Sharari, Sanaa P1-189
- Sharif, Sahar FC9.5
- Sharipova, Madina P2-295
- Sharma, Shreya P2-22
- Shaw, Nick P1-172
- Shcherbak, Yuliya FC10.3, P2- 272
- Shefer Averbuch, Noa P1-291, P2-267
- Shehadeh, Naim P1-32
- Sheinvald, Sharon FC1.6
- Shen, Jian P1-90
- Shen, Linghua P3-12
- Shen, Tian P2-191
- Shen, Yiping P1-225, P1-277, P3-154
- Shen, Yongnian P1-277
- Shen, Yu P1-200
- Shepherd, Sheila RFC2.6
- Shestakova, Marina P1-209
- Shetty, Supreetha P2-211
- Shibata, Hironori P2-217
- Shibata, Hirotaka P1-275
- Shibata, Nao P1-173
- Shim, Kye Shik P3-103
- Shima, Hirohito P2-285, P3-27
- Shimizu, Chikako P1-243
- Shimura, Kazuhiro P1-290, P3-54
- Shin, Choong Ho FC5.3, LB-21, P1-431, RFC7.4, T10
- Shin, Jung Hyun P1-429
- Shin, Seung Han LB-21
- Shin, Sohyun P1-339
- Shin, Woo Chul P3-247
- Shine, Brian P3-299
- Shiran, Shelly P1-397
- Shiryeva, Tatiana P1-393
- Shiryeva, Tatyana P1-356
- Shlyachova, Natalia P1-13
- Shmalia, Mona P3-273
- Shmoish, Michael P1-53
- Shoji, Yasuko P1-416, P2-170, P2-252
- Shore, Tikva RFC10.6
- Shouval, Dror LB-25
- Shpitzer, Hana P1-187
- Shtamler, Anna P1-347
- Shu, Aimee FC14.4
- Shufang, Liu P3-323
- Shukareva-Angelovska, Elena P3-284
- Shukla, Ajay P1-280
- Shukla, Manoj P1-280
- Shukla, Rishi P2-73, P3-227
- Siahnidou, Soultana P1-118
- Siahnidou, Tania P1-198
- Sicre-Alonso, Silvia P2-118
- Sidorova, Yuliya P2-9
- Siebert, Reiner P1-51
- Sieniawska, Joanna P2-286
- Sifaqui, Sofia P2-46
- Siffroi, Jean-Pierre FC10.3
- Şiklar, Zeynep P2-137
- Silva, Wilson RFC13.4
- Silvano, Liliana P1-364
- Silve, Caroline P2-60
- Silvia, Fasoli P3-277
- Simatou, Aristophania P1-74, P2-40, P3-190
- Simmons, Ian RFC11.1
- Simmons, Jill H. P1-21, RFC2.1
- Simon, Albane P2-226
- Simon, Anna P1-169, P2-79
- Simon, Dominique RFC3.2
- Simoneau, Gabrielle P1-197, P1-57
- Simsek Kiper, Pelin Ozlem P2-59
- Simunovic, Marko P1-310
- Simões, Ana Sofia LB-16, P3-315
- Singer, Dana P1-397
- Sinha, Ajay P1-102
- Şiraz, Ülkü P3-134
- Sircili, Maria Helena P1-270, P3-219
- Siri, Giulia P1-391
- Sirikci, Onder P1-162
- Siuffi, Mirey P3-199
- Skakkebæk, Niels Erik T4
- Skarakia, Nikitas P1-74
- Skarakis, Nikitas P2-40, P3-190
- Skiadopoulos, Spyros P3-68
- Skopkova, Martina P2-91
- Skordis, Nicos P1-334, P1-394, P2-275, RFC8.3
- Skorilas, Andreas FC1.3
- Skorodok, Yulia P1-361, P2-221

- Skrbic, Roko P1-310
 Skrbic, Veselin P1-310
 Skrinar, Alison FC2.1, FC2.2, RFC2.1
 Skupień, Jan P3-317
 Skuse, David P1-375
 Slavakis, Aris P1-166
 Slezak, Ryszard LB-19
 Slowikowska-Hilczer, Jolanta P1-269
 Smeets, Dominique RFC12.1
 Smerieri, Arianna FC3.2
 Smith, Bernard Rees P2-293
 Smith, CJ RFC13.5
 Smith, Grant P1-35
 Smyczyńska, Joanna P1-355, P2-242
 Smyrnaki, Pinelopi P3-192
 Smyth, Arlene RFC3.1
 Snajderova, Marta FC12.2, RFC14.2, RFC6.6
 Sng, Andrew Anjian P1-44, P3-1
 Soare, Iulia P1-202
 Soares, Joana P3-239
 Soblet, Julie P1-86
 Sobngwi, Eugene P3-125
 Sobral, Lays RFC13.4
 Sobrero, Gabriela P1-364
 Sobrier, Marie Laure RFC8.2
 Sogi, Chisumi P2-285
 Sohn, Young Bae P2-175, P2-184
 Sokal, Etienne T9
 Sol, Bupo P1-240
 Solari, Sandra P2-46
 Soldatovic, Ivan P1-369
 Soliman, Aliaa P2-87
 Soliman, Ashraf P3-165
 Soliman, Ashraf P2-98
 Soliman, Ashraf P1-313, P2-156, P2-183, P2-296, P2-43, P2-50, P3-138, P3-139, P3-153, P3-160, P3-161, P3-28, P3-50, P3-74
 Soliman, Ashraf Tawfik P1-381, P2-11, P2-193, P2-71, P3-152, P3-185, P3-188
 Soliman, Hend P1-34, RFC7.3
 Solis, Mario RFC1.4
 Solntsava, Anzhalka P1-230, P2-111, P3-191, P3-312
 Solntseva, Angelica P2-172
 Sommer, Grit P1-164, P1-309
 Song, Ari P2-282
 Song, Jung Hup P3-34
 Song, Junghan T10
 Song, Kyungchul FC8.6
 Song, Wenjie FC14.4
 Song, Yanning P1-263
 Soranna, Davide P1-120
 Sorapipatcharoen, Kinnaree P2-26
 Soriano-Guillén, Leandro P2-23, P3-99
 Sorkina, Ekaterina P1-55
 Sorokin, Daniil P1-332
 Sotillos, Sol FC10.2
 Sotiridou, Ellada P2-143, RFC9.5
 Soto, Julio P1-399
 Soua, Habib P3-91
 Soucek, Ondrej FC6.3, LB-27
 Souieky, Fatima P1-381, P3-28
 Souikey, Fatima P2-193
 Sousa, Bebiana P2-107
 Sowada, Nadine P1-51
 Soysal Acar, Azime Şebnem P2-103
 Sozaeva, Leila P1-165, P2-9
 Spada, Caterina P1-68
 Spehar Uroic, Anita P1-36, P2-10, P2-179
 Spiegel, Ronen P2-146
 Spiga, Ivana P1-420
 Spiliotis, Bessie P3-48, P3-68
 Spinoit, Anne-Françoise P1-261, P1-271
 Spinuzza, Antonietta P1-300, P1-346
 Spoudeas, Helen RFC11.1, RFC5.4
 Springer, Alexander P1-261, P1-271, P2-247, RFC10.1
 Scroll, Patrick FC10.5, P1-412, P2-271, RFC10.5
 Sprynchuk, Natalia P3-262
 Spyrou, George M P1-394, P2-275
 Sreedharan, Aravind Venkatesh P1-302
 Srinivas, Priyanka P3-171
 Stadler, Michael RFC10.2
 Stagi, Stefano P1-107, P1-194, P1-336, P1-362, P1-79, P2-181, P2-21, P3-43
 Stamatova, Ana P3-284
 Stanghellini, Ilaria T6
 Stanik, Juraj P2-110, P2-91
 Stankute, Ingrida P2-70
 Starzyk, Jerzy P3-280, P3-288, P3-317
 Starzyk, Jerzy B. P3-279
 Stasinaki, Aikaterini P3-84
 Stayber, Lana T12
 Stawerska, Renata P1-355, P2-242
 Steell, Lewis FC2.5
 Steers, Denise P1-279
 Stefanova, Elisaveta P3-108, P3-256
 Stein, Robert P2-110
 Stein, Ronnie P1-347, P2-1
 Steinbeck, Katharine RFC11.3
 Steinmetz, Lucas P2-57
 Steinmetz, Lucas P2-196
 Stella, Marcello P3-17
 Stelzl, Robert RFC15.5
 Stephenson, Alexandra P1-148
 Stergiotis, Stefanos P3-102, P3-126
 Stern, Eve RFC5.5
 Stern, Eve Z RFC7.5
 Steunou, Virginie FC12.1, RFC8.2
 Stevens, Adam FC12.4, FC12.5, FC12.6
 Stevenson, Brian P1-412
 Stihinamsuwan, Kochakorn P1-201
 Stikkelsbroeck, Nike FC12.3
 Stikkelsbroeck, Nike P1-269
 Stipančić, Gordana P3-231
 Stivel, Mirta P2-228
 Stoeva, Iva P1-153, P1-307
 Stoffers, Iris P2-257
 Stopa-Vaucher, Sophie P1-424
 Storbeck, Karl H. P1-162
 Storbeck, Karl-Heinz FC10.1, FC15.3
 Storey, Caroline RFC3.2
 Storr, Helen P3-167
 Storr, Helen L RFC14.4
 Stoupa, Athanasia P1-80
 Stoycheva, Rosica T13
 Stožek, Karolina FC5.2, P1-148
 Straetemans, Saartje P2-153
 Strakova, Veronika FC12.2
 Strebkova, Natalia P1-405
 Street, Maria Elisabeth FC3.2, RFC14.3
 Street, Maria Elizabeth P2-171
 Stubbe, Anita T7
 Stubbe, Maria P1-279
 Stylianou, Charilaos P1-334, P1-394
 Su, Chang P1-316, P2-177
 Su, Zhe P1-225
 Suarez, Martha P3-283
 Sucena, Silvia P1-199
 Sugihara, Shigetaka RFC1.1
 Suh, Byun-Kyu P3-174
 Suh, Byung Kyu P2-85
 Suh, Byung-Kyu P2-122, P2-166
 Suh, Byungkyu P1-233, P2-218, P3-117
 Suh, Jungwhan FC8.6
 Suh, Yongsuk FC8.6
 Sukarova-Angelovska, Elena P3-248
 Suliman, Sara P2-112
 Sultana, Perveen P1-314
 Sumnik, Zdenek FC12.2, FC6.3, RFC3.1, RFC14.2, RFC6.6, P2-69
 Sun, Chengjun RFC6.1
 Sun, Hui P2-294
 Sun, Jiapeng P2-222
 Sun, Manqing P2-81, P3-204
 Suntharesan, Janani P2-80, P3-322
 Suntharesan, Jananie P3-291, P3-304, P3-321
 Šuput Omladić, Jasna P1-109
 Suutela, Maria T15
 Suzuki, Atsushi FC5.6, P3-173
 Suzuki, Dai P2-285, P3-27
 Suzuki, Junichi P1-333
 Suzumura, Hiroshi P2-189
 Suárez, Juan FC14.3, RFC14.1
 Svedlund, Anna P1-22
 Sveroni, Konstantina P3-96
 Sverstiuk, Volodymyra P2-299
 Svigir, Alen P1-36
 Sweet, Ian RFC4.6
 Swolin-Eide, Diana P1-22
 Symonds, Michael E. P1-352
 Szalecki, Mieczysław p1-421
 Szałapska, Małgorzata P1-355
 Szczęrski, Jan P2-163
 Szinnai, Gabor FC7.2, P1-29
 Szmigiero-Kawko, Małgorzata P3-81

- Sztefko, Krystyna P3-288
 Sáez de Pipaón, Miguel P2-145
 Sánchez-Curiel Loyo, Mariana- P1-15
 Sánchez-Muñoz, Fausto P1-43
 Sävendahl, Lars FC14.5
 Söder, Olle P1-42, RFC14.5
 Sönmez, Alev Aldemir P3-250
 Sözungüzel, Mavi Deniz P1-145
 Siklar, Zeynep FC6.4, P3-8
- T**
 Tack, Lloyd P1-171, P1-261, P1-271, P2-105, RFC8.6
 Tadgell, Shawn P2-151
 Tagi, Veronica LB-13
 Tahir, Aisha P3-310
 Tahri, Abir P3-142, P3-148
 Taibi, Ludmila P2-251
 Tait, Sabrina P1-260, P1-58
 Takada, Shuji FC3.1
 Takagi, Masaki P1-115
 Takahashi, Ikuko P1-290
 Takase, Kaoru P2-249
 Takeyari, Shinji P1-168
 Takishima, Shigeru P3-54
 Takubo, Noriyuki P1-243, P1-290
 Talarico, Valentina P2-300
 Talat, Nabila P3-310
 Talucci, Giovanna P1-68
 Tam, Yuk-him P3-246
 Tamai, Shinya P2-217
 Tamaro, Gianluca P1-360
 Tamaşanu, Raluca Corina P2-116
 Tamburino, Federica P1-378, P3-164
 Tamme, Reeli P1-17
 Tamura, Takuya RFC3.4
 Tan, Aykut P2-291
 Tan, Cagman P1-239
 Tan, Daisy FC10.3
 Tan, Jun Guan P2-41
 Tan, Xin T20
 Tan, Xinrui P2-191
 Tanaka, Tatsushi FC5.6, P3-173
 Tanaka, Yukari P2-230
 Tangari Saredo, Ana P1-240
 Tani, Tomoyuki P2-249
 Tanja, Diana P1-148
 Tankoska, Maja P3-284, P3-307
 Tanteles, George A P1-334, P1-394
 Tanik, Canan P2-255
 Tapia, Alejandra P1-338
 Taranu, Ioana P3-109
 Tarim, Omer P1-329
 Tarkkanen, Annika P1-395, T15
 Taruscio, Domenica RFC3.1
 Tasic, Velibor P2-216
 Tassinari, Roberta P1-260, P1-58
 Tastan, Mehmet RFC15.2
 Tatar, Abdulgani P2-42
- Tateyama, Michihiro FC5.6
 Tatli, Zeynep Uzan P2-169
 Tatsi, Elizabeth-Barbara FC1.3, P1-118
 Tauber, Maithé P1-139
 Tauber, Maithé P1-150
 Tauschmann, Martin P1-179
 Tavares, Cláudia P3-157
 Tawfik, Sameh P3-168
 Tay, Vanerry LQ P2-16
 Tayeb, Tara P2-63
 Tayeb, Tara Hussein P1-317
 Tayebi, Youcef P3-113
 Taylor-Miller, Tashunka P2-152, P2-253
 Tebib, Neji P2-77
 Teilmann, Grete P1-114
 Teinturier, Cécile P1-213
 Tekin Orgun, Leman P2-103
 Tena-Sempere, Manuel PL5
 Tenenbaum, Ariel P1-291, T17
 Tenenbaum-Rakover, Yardena P1-105, P1-430, P2-146, P2-19, P2-244, P3-200
 Tenoutasse, Sylvie P2-153
 Teodori, Caterina P1-79
 Teofoli, Francesca P1-5, RFC9.3
 Tepeli, Emre P2-51
 Terashita, Shintaro P1-406
 Terzi, Cesare P2-150, P3-133
 Tessaris, Daniele MTE 5, P1-20, P1-400, P1-422, P3-30
 Testa, Graciela P1-364
 Tezcan, Ilhan P1-239
 Thakker, Rajesh P2-36
 Thalange, Nandu P2-17
 Thalassinos, Caroline P1-80, P2-226
 Thankamony, Ajay RFC14.5
 the I-DSD consortium, On behalf of RFC8.6
 Theodoropoulou, Eleni P3-101
 Thi Bich Ngoc, Can P2-133, P3-141
 Thi Nhu Hoa, Pham P3-141
 Thi Thanh Mai, Do P2-133, P3-141
 Thiele, Susanne T7
 Thireos, Eleftherios P2-140
 Thodberg, Hans Henrik FC2.6, RFC2.3, RFC2.3
 Thomas, Muriel P2-153
 Thomas, Nick P2-231, RFC11.1
 Thomas, Sophie RFC11.1
 Thomazini Dallago, Renata P1-85
 Thorley, Emma P1-104
 Thornton, Paul FC14.4
 Thorp, Nicola P1-102, P1-259
 Thorpe, Nicola RFC11.1
 Thu Ha, Nguyen P3-141
 Thyen, Ute P1-269
 Tiberi, Lucia P1-336, P1-362, P2-181
 Ticha, Lubica P2-168
 Tidblad, Anders P2-162
 Tiedemann, Karin FC3.5
- Tikhonovich, Yulia P1-55
 Tikka, Maria P3-48
 Tilleman, Kelly P1-271
 Tillmann, Vallo P1-17, P1-289
 Tim-Aroon, Thipwimol P2-26
 Timmermann, Beate P1-398
 Timmers, Henri RFC2.5
 Timpanaro, Tiziana P1-247, P2-75, P3-5
 Ting, Teck Wah P1-302
 Tiosano, Dov P1-4
 Tirosh, Amir FC1.6
 Tiulpakov, Anatoly FC11.4, P1-55, P1-206, P1-332, P1-415, P2-157, P2-250, P2-35
 Tjahjono, Harjoedi Adj P3-326
 Tobias, Edward S RFC10.3
 Tobias, Leraz P1-430
 Todorova, Zdravka P3-108, P3-256
 Todorovic, Sladjana P1-369
 Toffoli, Barbara LB-18
 Toffoli, Carlotta RFC7.6
 Tokarska, Agnieszka P1-373
 Toki, Machiko P1-140
 Toksoy, Guven P1-134, P1-306, P2-5
 Toksoy, Güven P1-390, P2-195
 Tolstikova, Olena P2-200, P3-110, P3-122
 Tomlinson, Jeremy P1-10, P1-167
 Toni, Ledjona RFC14.2, RFC6.6
 Tonnhofer, Ursula P1-261, P1-271, P2-247
 Tonon, Federica LB-18
 Toni, Giacomo P2-227
 Topal, Neval P1-283
 Topaloglu, A. Kemal RFC15.2
 Topaloglu, Ali Kemal RFC8.5
 Topaloglu, Ali Kemal P1-117, P1-411
 Torky, Ahmed P2-256
 Tornese, Gianluca LB-18, P1-111, P1-360, P2-171, P3-168, P3-244
 Tornese, Virginia P2-90
 Tornicasa, Vincenzo P2-159
 Tornincasa, Vincenzo P1-220
 Toromanovic, Alma P2-48
 Torpy, David P1-299
 Torrecilla-Parra, Marta FC8.4
 Torres Lacruz, Marisa P1-282
 Torres LaCruz, Marisa P3-107
 Torres Tamayo, Margarita RFC1.3
 Tortora, Domenico RFC12.5
 Torun, Emel P1-396
 Toumba, Meropi P1-334, P1-394, RFC8.3
 Touraine, Philippe P2-226
 Tournier, Andrea P1-8
 Touzon, Maria Sol P1-129, P2-259
 Toye, Kaatje P2-105
 Trabado, Séverine FC2.3, P1-23
 Traficante, Giovanna P1-194, P1-336, P2-181
 Tragomalou, Athanasia P3-101, P3-96

- Trajanova, Despina P1-149
 Tran, Huyen P3-313
 Travieso-Suárez, Lourdes P1-100
 Tremblay, Angelo P1-197, P1-57
 Trevisan, Marina P1-360
 Triador, Lucila P1-49
 Triantafyllou, Konstantinos P2-214
 Triantafyllou, Panagiota P1-166
 Tridenti, Gabriele P2-150, P3-133
 Tripathi, Archana P1-280
 Tripto-Shkolnik, Liana LB-25
 Tromp, Ellen RFC13.3
 Trujillano Lidón, Laura P1-229
 Trunin, Yuri FC11.5
 Truong, Thi Phuong Uyen P3-213
 Tsang, Anita MC P3-100
 Tsargasova, Irina P3-55
 Tsatsoulis, Agathocles P1-54
 Tseretopoulou, Xanthippi P2-248
 Tsikopoulos, Georgios P3-184
 Tsinopoulou, Vassiliki Rengina P2-301
 Tsochev, Kaloyan T13
 Tsuboi, Yayoi P2-189
 Tsukano, Shinya P3-63
 Tuli, Gerdi P1-20, P1-400, P1-401, P1-422, P2-208, P3-30, RFC5.1
 Tulpakov, Anatoliy P2-245
 Tun, Hein P1-49
 Tuncerler, Gülten P1-335
 Tuney, Davut P3-202
 Tung, Joanna YL P3-100
 Turan, Hande P2-5
 Turan, Ihsan RFC15.2, RFC8.5
 Turan, Serap P1-159, P1-162, P1-175, P1-176, P1-273, P1-402, P1-53, P2-25, P2-52, P3-202, P3-80
 Turan, Serap P1-116, P1-3
 Turchina, Svetlana P1-13
 Turkunova, Maria P2-221
 Turkunova, Mariia P3-150, P3-55
 Tutar, Engin P3-202
 Tutunculer, Filiz P1-162
 Tuysuz, Beyhan P2-5
 Twig, Gilad P2-123
 Tychalas, Athanasios P2-301
 Tyutyusheva, Nina HDI 2.1, HDI 2.1
 Tzur, Dorit P2-123
 Türkyılmaz, Ayberk P1-241
 Tüysüz, Beyhan P2-137
 Tämäşanu, Raluca Corina P3-303
 U
 Ubertini, Graziamaria P1-14, P1-401
 Ubertini, GraziaMaria P1-386
 Ucakturk, Seyit Ahmet P1-255
 Uday, Suma P1-172, RFC6.5
 Ulivi, Sheila LB-22
 Ullah, Irfan P1-222, P3-20, P3-76
 Ullah, Irfan Ullah P1-11
 Ulman, İbrahim P3-217
 Umano, Giuseppina Rosaria FC4.4, P1-354, P1-45
 Umeki, Ikumi P2-285, P3-27
 Umino, Satoko P2-230
 Unal, Edip P1-254, RFC15.2
 Unal, Edip P1-91
 Unic, Ivana P1-310
 Unsal, Yagmur P1-239, P2-59
 Ünver Tuhan, Hale LB-14, P3-268
 Upners, Emmie N FC14.2
 Urakami, Tatsuhiko P1-333, RFC1.1, S9.2
 Ursi, Davide P1-354
 Urszula, Smyczynska P1-77
 Usheva, Nataliya P1-350
 Ushijima, Kikumi RFC1.1
 Uslu, Inayet Nur P1-117
 Utine, Eda P2-59
 Uyanik, Rukiye P3-8
 Uyguner, Oya P1-134, P1-306, P2-195
 Uyguner, Zehra Oya P1-159, P1-390, P2-5
 Uzan Tatlı, Zeynep P3-67
 Uzan Tatlı, Zeynep P1-244, P3-134, P3-263
 Uzun, Hamide P1-335
 Uzun, Selin P3-217
 Uzunkopru, Gizem P2-240
 Uçar, Ahmet P2-255
- V**
- V. Zhukouskaya, Volha RFC2.2
 Vad, Knud P1-371, RFC14.6
 Vaiani, Elisa P1-249
 Vaisbourd, Julia P1-59
 Vakaki, Marina P1-432
 Vakili, Rahim P2-202
 Valentini, Denis P1-360
 Valenzise, Mariella P2-147, P2-186, P3-164, RFC5.1
 Vallespín, Elena RFC1.4
 Valsassina, Rita P3-239
 Valteau-Couanet, Dominique P2-226
 Valuniene, Margarita LB-9
 van Alfen-van der Velden, Janielle FC12.3
 van Beijsterveldt, Inge P2-126
 van Beijsterveldt, Inge ALP P1-52
 van Boxel, Elizabeth-Jane P3-299
 van de Grift, Tim P1-269
 van den Akker, Erica P1-196, P1-46, P1-47, RFC13.3
 van den Berg, Sjoerd P1-158, P1-367, P1-7
 van der Grinten, Hedi Claahsen RFC10.1
 van der Kaay, Danielle P1-223
 van der Kamp, Hetty P1-10
 van der Lely, Aart Jan FC8.3
 van der Linde, Annelieke P1-157, P1-92
 van der Schoor, S.R.D. RFC9.2
 van der Straaten, Saskia RFC8.6
- van der Velden, Janielle P1-377, RFC12.1
 van der Velden, Janielle P1-388
 van der Voorn, Bibian FC13.2, FC13.4, P1-46, P1-47
 Van der Werf-Grohmann, Natascha P2-32
 van Dijk, Tessa P1-228
 van Dommelen, Paula P1-220, P1-221
 van Doorn, Jaap P1-367
 van Duyvenvoorde, Hemine P1-223
 van Duyvenvoorde, Hermine A. P1-228
 van Haelst, Mieke P1-46, P1-47
 Van Haelst, Mieke P1-196
 van Haeringen, Arie P1-223
 Van Heerden, Carel Jacobus P1-1
 van Heteren, Cathelijne LB-12
 Van Hoecke, Eline P1-261
 Van Hulst, Andraea P1-197, P1-57
 van Keulen, Britt FC13.2
 Van Laecke, Erik P1-261, P1-271
 Van Lancker, Sophie P1-171
 Van Leeuwen, Evert P1-377
 Van Maldergem, Lionel FC10.3, P1-127
 van Rijswijk, Joukje LB-12
 van Rossum, Elisabeth P1-46, RFC13.3
 van Tellingen, V. RFC9.2
 van Trotsenburg, A.S.P. RFC9.2
 Van Trotsenburg, Mick S6.3
 Van Vliet, Guy FC5.4, P1-425
 Van Welie, Nienke LB-12
 Van't Hoff, William FC2.1, FC2.2
 Vandekerckhove, Kristof P2-105
 Vander, Shelly P1-361
 Vanderroost, Juliette T9
 Vanderwert, Fiorenza Irushani P1-362
 Vanegas, Sara P3-186, P3-199
 Vanhaesebrouck, Sigrid P2-136
 Vannelli, Silvia RFC11.2
 Varga, Lukas P2-91
 Vargas, Antonio FC14.3, RFC14.1
 Vargha-Khadem, Faraneh RFC11.1
 Varin, Thibaut P1-197, P1-57
 Varini, Susanna P1-378
 Varriale, Gaia P2-21
 Vasanwala, Rashida Farhad P1-302
 Vasilache, Simona P1-358
 Vasilakis, Ioannis Anargyros P1-118
 Vasiliev, Evgeniy P1-415
 Vasiliev, Evgeny P2-35
 Vasilyev, Evgeniy P1-55, P2-250
 Vasilyev, Evgeny FC11.4, P1-332
 Vasiukova, Olga P1-55
 Vassart, Gilbert FC8.5
 Vasyukova, Olga P1-405
 Vecchiola, Andrea P1-338
 Vela, Amaia P2-254, P2-279
 Velcean, Alexandra Maria P3-303
 Venara, Marcela FC14.1, P1-359
 Ventresca, Silvia P3-17

- Ventura Wichner, Paula Sol P1-282, P3-107
 Verdecchia, Federica P3-266
 Vergani, Debora P1-336, P1-362, P2-181
 Vergier, Julia P3-269
 Verhoeve, Harold LB-12
 Verkauskas, Gilvydas RFC10.2
 Verkauskiene, Rasa LB-9, P2-70
 Verloes, Alain P1-139
 Vestergaard, Esben T P1-136
 Vestrucci, Benedetta P2-227
 Viaud, Magali P1-80, P2-176
 Viazava, Liudmila P3-312
 Vicel, Beate RFC10.2
 Vick, Philipp FC5.5
 Vieira, Paula LB-16, P3-315
 Vieites, Ana P1-10, P1-157
 Vigone, Maria Cristina P1-420, P1-423, P2-298
 Vilain, Catheline P1-86, P2-237
 Villafañ-a-Rauda, Santiago P1-43
 Villanueva-Ortega, Erendira P3-286
 Villarroya, Francesc FC4.3
 Vincenzi, Gaia P1-420, P1-423, P2-298
 Vincenzi, Monica P1-5, RFC9.3
 Vinci, Federica P1-323, P1-428, P2-64, P3-115, P3-98
 Vinci, Francesco P1-251
 Viner, Russell RFC11.3
 Vink, Denise RFC11.6
 Vinkovic, Maja P2-10
 Viola, Anna P2-8
 Virdis, Raffaele P2-150, P3-133
 Virtanen, Heidi P1-9
 Visser, W. Edward RFC3.1
 Vitale, Laura P1-8
 Vitebskaya, Alisa P3-166
 Viterbo, Gisela P1-249
 Viuff, Dorthe P1-235, P1-84
 Vlachakis, Dimitrios FC13.6
 Vlachopapadopoulou, Elpis FC14.4, P1-432, P2-251
 Vlachopapadopoulou, Elpis Athina P1-96
 Vlachopapadopoulou, Elpis-Athina P3-102, P3-126
 Vlachou, Thomas P3-236
 Vladimirova, Victoria P2-212
 Vlahos, Antonios P1-54
 Vlahova, Diana P1-307
 Voet, Bernard P1-156, P1-157
 Vogt, Josef RFC7.2
 Volevodz, Natalya P1-209, P1-356
 Volkan, Burcu P3-202
 Vollbach, Heike RFC11.5
 Volodko, Elena P1-121, P3-242
 Von Borries, Denise P1-37
 von Schnurbein, Julia P1-51, RFC11.5, RFC7.2
 Von Schulz Hausmann, Cristian P1-82, P2-167
 von Sengbusch, Simone P1-179
 Vorontsov, Aleksandr P2-212
 Vorozhko, Oksana P2-221
 Vorster, Anna Alvera P1-1
 Vosáhlo, Jan P2-69
 Voutetakis, Antonis P1-154
 Vrbicka, Dita LB-27
 Vu Chi, Dung P3-21, P3-260
 Vu, Chi Dung P2-7
 Vulic, Luka P1-310
 Vuralli, Dogus FC15.2, P1-404, P1-71, P2-223, P2-224
 Vuralli, Dogus P1-239, P2-59
 Vyazmenov, Edward RFC5.3
 Vázquez, Javier Garcia LB-20
 Vázquez, Rocío P3-119
 Vázquez, Élida P2-164
 Vázquez-Cobela, Rocío P1-345
- W**
- Wabitsch, Martin P1-210, P1-51, RFC11.5, RFC7.2
 Wada, Soichiro P2-30
 Wafa, Ehsan P1-413
 Wagih Darwish, Yasser RFC1.6
 Wagner, Gudrun P2-187
 Wagner, Isabel Viola P1-42
 Walad Dhawi, Naji P1-11
 Walczak, Mieczysław P1-387, P1-87
 Waldner, Richelle P1-427, P3-234
 Walenkamp, Marie-Jose HDI 2.2
 Wali, Yasser P1-11
 Walker, Amy FC9.1, P1-311
 Walker, Brian FC13.2
 Wall, Meaghan P1-124
 Walsh, Elizabeth P1-25
 Walter, Jens P1-49
 Waly, Sherif P2-256
 Wang, Chunlin FC1.1, P1-278, P1-297, P2-121
 Wang, Chunling P3-223
 Wang, Defen P2-81, P3-204
 Wang, Hongsheng P1-186
 Wang, Huizhen P3-12
 Wang, Jian P1-225, P1-277, P2-177, T20
 Wang, jian P2-188
 Wang, Junqi T11
 Wang, Lishun RFC6.1
 Wang, Marcia P1-199
 Wang, Min P3-265
 Wang, Rong P1-4
 Wang, Rui P1-316
 Wang, Wei P2-81, P3-204, P3-261, T11
 Wang, Xiaoyan P3-208
 Wang, Xin-li P3-145
 Wang, Xiumin P1-225, P1-277, P2-188, T20
 Wang, Xu RFC6.1
 Wang, Yirou P1-225, P1-277, P2-188
 Wankanit, Somboon P2-131
 Wannes, Salmane P3-91
 Wannes, Selmen P2-60
 Ward, Leanne RFC2.1, S2.3
 Warmuth-Metz, Monika P1-398, P1-99
 Warner, Justin P1-327
 Warr, Nigel FC10.3
 Warren, Daniel RFC11.1
 Wasniewska, Małgorzata P1-300, P1-346, P1-422, P1-53, P2-147, P2-171, P2-182, P2-232, P3-10, P3-164, P3-209, RFC5.1
 Wasniewska, Małgorzata Gabriela P3-232
 Wasyl-Nawrot, Barbara P3-317
 Watanabe, Satoshi FC3.4, P1-170
 Watanabe-Yamamoto, Sayaka P3-54
 Watkins, Alice P1-375
 Wattanasirichaigoon, Duangrurdee P2-26
 Weber, Astrid P1-246
 Weber, Giovanna P1-420, P1-423, P2-298, P3-144, P3-205
 Weber, Karin P1-12
 Weber, Michael FC2.4
 Weerasinghe, Kamal P2-290
 Wegmann, Mathilde Gersel RFC14.5
 Wehkalampi, Karoliina FC8.5
 Wei, Haiyan P2-55, P3-12
 Weinberg-Shukron, Ariella RFC10.6
 Weinberger, Jeffrey P2-146
 Weintrub, Naomi P1-265, P2-1
 Weiss, Batia LB-25
 Weiß, Birgit FC5.5
 Welsch, Sophie T9
 Wen, Sun P1-219
 Weng, Ying P3-158
 Weninger, Julia P1-261, P1-271
 Wenn, Melanie P2-108, P3-104
 Werdani, Amina P2-60
 Werner, Ralf RFC10.4, T7
 Whalen, Philip FC15.1
 Whalen, Sandra P1-218
 Whatmore, Andrew FC12.4, FC12.5, FC12.6
 Whitaker, Martin P1-156
 Whyte, Michael P. FC2.1, FC2.2, RFC2.1
 Wicart, Philippe FC2.3
 Wiechers, Cornelia P2-144
 Wiegand, Susanna P1-156
 Wieland, Ilse FC9.6
 Wiemann, Dagobert FC7.6
 Wiemann, Stefan FC5.5
 Wiepjes, Chantal RFC11.6
 Wikiera, Beata RFC12.2
 Wild, Cervantée P1-50
 Willem, Marjorie FC12.1
 Williams, Alistair J.K. FC1.5
 Williams, Georgina FC1.5

- Williams, Jack FC13.5, RFC14.4
 Williams, Mark P1-65
 Wilne, Sophie RFC11.1
 Wiltshire, Esko P1-279
 Wintergerst, Uwe RFC15.5
 Wit, Jan M P1-221
 Wit, Jan Maarten RFC2.5
 Wit, Jan-Maarten P1-228
 Witkowska-Sędek, Ewelina P1-73, P2-93
 Witsch, Michael FC7.6
 Woelfle, Joachim FC9.4, P1-212, P1-214
 Wolstencroft, Jeanne P1-375
 Won, Sehoon FC15.1
 Wong, SL Jeanne P2-292
 Wong, Sze C. FC2.5
 Wong, Sze Choong P1-125, RFC2.6
 Wong, Sze Lyn Jeanne P1-403
 Wood, Claire FC5.1, MTE 7
 Woodhead, Tricia P1-327
 Woodward, Mark P2-253
 Worth, Austen RFC5.4
 Wu, Wei RFC1.5
 Wu, Bingbing P2-95
 Wu, Di P3-145, P3-154
 Wu, Di P1-316
 Wu, Haiying P3-208
 Wu, Jing RFC6.1
 Wu, Shengnan P2-55
 Wu, Wei P1-200, P2-246, P2-29
 Wu, Xiaohui RFC12.4
 Wu, Xiaohui RFC4.5
 Wudy, Stefan P2-66, P3-4
 Wudy, Stefan A. P1-53, S7.3
 Wudy, Stefan A. FC9.4, P1-12, P1-158,
 P1-2, P1-301, P1-4, P1-7
 Wurm, Michael P2-32
 Wynter, Lisa P1-50
 Wysoczanska-Klaczynska, Anna LB-19
 Wójcik, Małgorzata P3-280
 Wójcik, Małgorzata P3-279, P3-288,
 P3-317
 Wójtowicz, Jerzy P2-36
 Wölflé, Joachim P1-234
- X**
 Xargay-Torrent, Silvia FC9.3, P1-56,
 P2-127, RFC4.3
 Xargay-Torrent, Sílvia P1-193
 Xekouki, Paraskevi P3-192
 Xenopoulou, Theodora P3-236
 Xi, Li P2-95, P3-197, P3-24
 Xiao, Yanfeng LB-10, P3-265
 Xiao, Yuan P2-81, P3-204, P3-261
 Xiawudong, Adaleti P3-14
 Xie, Rongrong P3-208
 Xie, Yiwen T11
 Xinhui, Han P1-219
 Xiong, Feng P2-121
 Xu, Jing P1-304
- Xu, Yufei P1-225, P1-277, P2-188
 Xuefei, Chen P3-169
- Y**
 Y Nishi, Mirian P1-135
 Yackobovitch-Gavan, Michal T17
 Yaden, Youssef P3-240
 Yaghmaie, Bahareh P1-146
 Yakar, Omer P3-235
 Yakovenko, Vira P2-269
 Yalcin, Koray P2-235
 Yalın Sapmaz, Şermin P3-285
 Yamaguchi, Naoya P3-173
 Yamaguchi, Takeshi P3-54, RFC9.1
 Yamaguchi, Tomoe P1-406
 Yamamoto, Kenichi P1-168
 Yaman, Ali P1-3
 Yamaguchi, Naoya FC5.6
 Yamoto, Kaori T16
 Yang, Eun Mi P1-368
 Yang, Haihua P3-12
 Yang, Jung Dug P3-305
 Yang, Lili P1-343, P1-90
 Yang, Lin P3-32
 Yang, Rongwang P1-90
 Yang, Sei Won LB-21, RFC7.4, T10
 Yang, Seung P1-174, P1-372, P1-75
 Yang, Xi P2-246
 Yang, Xiaohong P1-191, P1-224, P1-63
 Yang, Yi RFC6.1
 Yang, Yu P3-145
 Yanlan, Fang RFC5.6
 Yanovski, Jack A. FC15.1
 Yao, Ruen P1-277, T20
 Yarali, Oğuzhan P1-241
 Yarhere, Iroro P3-294
 Yarhere, Iroro P3-311
 Yarim, Gul Fatma P1-255
 Yart, Armelle P1-139
 Yasmine, Ouarezki P1-292, P2-161
 Yassin, Haytham P3-152
 Yassin, Khadra P3-185
 Yassin, Mohamed P3-185, P3-188
 Yatsenko, Svetlana P1-142
 Yatsuga, Shuichi P2-230
 Yau, Daphne P1-205
 Yau, Ho-chung P3-246
 Yavas Abali, Zehra P1-3, P1-159, P1-175,
 P1-176, P1-273, P2-52, P3-202
 Yavas Abali, Zehra P1-402, P3-80
 Yazawa, Takuya FC5.6
 Ybarra, Marina P1-199, P1-337, P1-39
 Ye, Lei P3-261
 Ye, Minyi P3-241
 Yel, Servet P2-198
 Yeshayahu, Yonatan RFC5.5
 Yesiltepe-Mutlu, Gul P2-240
 Yesquen, Pamela P2-164
 Yeste, Diego P2-164
- Yetkin Ay, Zuhal P2-291
 YH Hong, Janet P2-292
 Yi, Kyung Hee P1-174, P1-75, P2-241,
 P3-172
 Yi, KyungHee P1-372
 Yi, Yajun P1-316
 Yildirak, Ekrem P3-3
 Yildirim, Nurdan P2-101
 Yildirim, Ruken RFC15.2
 Yildiz, Duran P1-71
 Yildiz, Melek P1-134, P1-159, P1-162,
 P1-248
 Yildiz, Melek P1-283
 Yilmaz, Gulay C. P1-162
 Yilmaz, Mehmet Bertan P1-117, P1-237
 Yin, Chunyan LB-10
 Ying, Yanqin P2-246
 Yiğit Gülşahin, Elif P3-106
 Yiğit, Özgül P1-294
 Yokota, Ichiro RFC1.1
 Yokoya, Susumu LB-1, P1-243
 Yoo, Chaeri P2-165, P2-78
 Yoo, Eun-Gyong P2-165, P2-78
 Yoo, Han-Wook P1-101, P2-209,
 P3-179
 Yoo, Jae-ho LB-23
 Yoon, Ju Young P1-385, P1-62, P3-13
 Yordanova, Desislava P3-108, P3-256
 Yordanova, Nikolinka P2-174
 Yorifuji, Tohru P1-243
 Yorifuji, Toru P1-173
 Yoshida, Aya FC5.6, P3-173
 Yoshida, Kei P1-333
 Yoshihara, Shigemi P2-189
 Yoshii, Keisuke P1-406
 Yoshiura, Koh-ichiro FC3.4
 Younes, Maha P1-215
 Yousry, Yousra P1-413
 Yu, Jeesuk P1-184, P3-64
 Yu, Tingting P1-277
 Yu, Xiao P2-246
 Yu, Yong FC15.2
 Yu, Yunxian P1-200
 Yuan, Jinna LB-24, P1-200, P2-29,
 RFC4.2
 Yuan, Xin P1-191, P1-224, P1-63
 Yuan, Yuan P3-323
 Yuanyuan, HE P1-219
 Yuditskiy, Anton P1-78, P2-185
 Yue, Shanna FC15.1
 Yukhлина, Yulya P1-256
 Yuksel, Bilgin P1-411
 Yuksel, Bilgin RFC15.2, RFC8.5
 Yuksel, Sahika P2-270
 Yunqi, Chao P2-135
 Yusipovich, Alexander P1-393
 Yüce Kahraman, Çiğdem P2-42
 Yıldırım, Ruken P1-207
 Yıldız, Melek P1-207

Z

Zabransky, Markus P1-227, P1-387, P1-87, P2-178
Zacharin, Margaret FC3.5
Zachurzok, Agnieszka P1-131
Zadik, Zvi P1-361
Zahade, Fouad P1-128
Zaharia, Cristina P1-202
Zahir, Bouzrar P2-161
Zaid, Mahdi P3-45
Zaihra, Tasneem P1-337
Zain, Fuziah P1-403
Zajdel-Cwynar, Olimpia P1-41
Zakaria, Rosita P1-158, P1-7
Zakharova, Ekaterina P1-69
Zalmon-Koren, Ilana P3-281
Zambon, Antonella P1-120
Zamir, Gershon Goor P2-146
Zangen, David RFC10.6
Zangen, David FC11.3, P1-128, RFC3.3
Zapletalova, Jirina LB-27
Zappitelli, Michael P1-197, P1-57
Zargni, Asma P2-266
Zaytseva, Elena P3-312
Zebian, Bassel RFC11.1
Zec, Ivana P3-231
Zeevaert, Renate P2-136
Zeino, Mazen P1-281
Zeligson, Sharon P1-128
Zelinska, Nataliya P2- 272, P2-281, P3-237
Zemkova, Dana FC12.2

Zenaty, Delphine RFC3.2
Zenker, Martin FC9.6
Zerah, Michel P2-226
Zhang, Cai P2-54, RFC1.5
Zhang, Dandan P3-208
Zhang, Jianwei RFC4.1, P2-27
Zhang, Jingjing FC15.2
Zhang, Jun P3-241, P3-44
Zhang, Jun P3-6
Zhang, Jun P2-114, P3-193, P3-222
Zhang, Jun P3-151
Zhang, Li P1-200
Zhang, Lidan P2-81, P3-261
Zhang, Lina P2-68
Zhang, Lina P1-182, P3-89
Zhang, Lina P1-183, P1-232, P2-197
Zhang, Miaoying P2-95
Zhang, Wenting RFC4.5
Zhang, Xingxing P2-191
Zhang, Ying P1-191, P1-224, P1-63
Zhang, Yuanyuan P1-61
Zhang, Zhixin P3-272, P3-292
Zhao, Yue P2-246
Zhao, Zhengyan P1-90
Zhao, Zhuhui P2-95
Zheludkova, Olga P1-405
Zhelyazkova, Nikolina P3-95
Zheng, Zhangqian P3-197, P3-32
Zhiemuratova, Gulshad P2-295
Zhou, Bo P3-272, P3-292
Zhou, Shanggen P1-21
Zhou, Xuelian P2-29, RFC4.2
Zhu, Jianfang P1-297, P3-223
Zhu, Mingqiang P2-29

Zhu, Yilin P1-278, P3-223
Zhukouskaya, Volha FC2.3, P1-18, P1-23
Zhukovskaya, Elena P2-109
Zhuravlev, Vladimir P3-191
Ziani, Z P2-280
Zielinska, Nataliya P1-361
Ziembas, Dominka P2-88
Zingg, Tanja Ch. P1-309
Zioutas, Maximiliano P2-92
Zirilli, Giuseppina P2-147, P2-186, RFC5.1
Zitzmann, Michael LB-3
Zoi, Vasiliki P1-198
Zorludemir, Unal P1-411
Zosi, Paraskevi P3-236
Zou, Chao-Chun P2-125
Zou, Chaochun P1-343, P1-90
Zou, Chaochun RFC12.4
Zouater, Hichem P1-227, P1-387, P1-87, P2-178
Zozulińska-Ziółkiewicz, Dorota P1-287
Zubkova, Natalia P1-332
Zubkova, Natalya P2-250
Zucchelli, Mino P1-106
Zucchini, Stefano P1-106, P1-401, P2-171, P2-232, P2-92
Zuckerman Levin, Nehama P1-32
Zumsteg, Urs FC7.2, P1-29
Zung, Amnon P1-295
Zwaveling-Soomawala, N. RFC9.2
Zyuzikova, Zinaida P1-209
Zöllner, Ekkehard Werner P1-1